

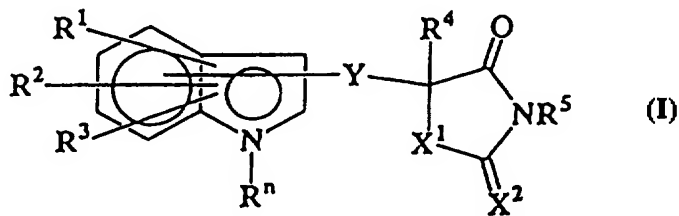


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(54) Title: THIAZOLIDINE AND OXAZOLIDINE INDOLES WITH HYPOCLYCEMIC ACTIVITY**(57) Abstract**

An indole type thiazolidine compound of formula (I) and its salt, wherein X^1 is S or O; X^2 is S, O or NH; Y is CR^6R^7 (R^6 is a hydrogen atom or a C_1 - C_7 alkyl group); R^1 is a substituent at the 2-, 3-, 4-, 5-, 6- or 7- position of an indole ring and is a C_1 - C_{10} alkyl group, $-W_k-V_l-Z$ (Z is a C_3 - C_{10} cycloalkyl group, a C_6 - C_{14} aromatic group, a C_1 - C_{12} heterocyclic aromatic group, a C_1 - C_6 heterocycloaliphatic group, etc., V is O, S, etc., W is a divalent C_1 - C_6 saturated or C_2 - C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1 - C_7 alkyl groups, and each of k and l is 0 or 1), $-V-W-Z$ (V, W and Z are as defined above), $-W-V-W-Z$ (V, W and Z are as defined above, and two W's may be the same or different), or R^1 may be a hydrogen atom when Y is bonded to the 4-, 5-, 6- or 7-position of an indole ring; each of R^2 and R^3 is a substituent at the 2-, 3-, 4-, 5-, 6- or 7-position of an indole ring, and is independently a hydrogen atom, a C_1 - C_7 alkyl group, or the like; R^4 is a hydrogen atom or a C_1 - C_7 alkyl group; R^5 is a hydrogen atom or a carboxymethyl group; and R^n is a substituent at the 1-position of an indole ring, and is a hydrogen atom, a C_1 - C_7 alkyl group, a C_1 - C_7 alkoxy group, an alkylsulfonyl group, an arylsulfonyl group, or the like.



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DESCRIPTION

THIAZOLIDINE AND OXAZOLIDINE INDOLES WITH HYPOGLYCEMIC ACTIVITY

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TECHNICAL FIELD

The present invention relates to novel indole type thiazolidines having a hypoglycemic effect and aldose-reductase inhibitory activities, which are useful in medical and veterinary fields, particularly useful for preventing or treating diabetes mellitus and diabetic complications.

BACKGROUND TECHNIQUE

Heretofore, various sulfonylurea derivatives and biguanide derivatives have been widely used as oral hypoglycemic agents for lowering blood sugar levels. However, these agents had disadvantages of causing serious hypoglycemic coma and lactic acidosis revelation, and therefore every possible care must have been taken for practical use. "Chem. Pharm. Bull., vol. 30, p. 3563 (1982)", "J. Med. Chem., vol. 32, p. 421 (1989)", "J. Med. Chem., vol. 34, p. 318 (1991)", "J. Med. Chem., vol. 33, p. 1418 (1990)", Japanese Unexamined Patent Publication No. 64586/1980, and European Laid Open Patent Publications No. 177353, No. 283035, No. 283036, No. 332331, and No. 332332 disclose various thiazolidindiones which achieve a hypoglycemic effect, and these are particularly useful for treating Type II diabetes and are

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noted as agents for hardly causing such hypoglycemic symptoms as caused by the above-mentioned oral hypoglycemic agents. However, although these compounds have a function of effectively lowering a blood sugar level, it is not proved that these compounds have effects for reducing or preventing various chronic symptoms caused by diabetes, such as diabetic nephropathy, diabetic cataract, diabetic retinopathy, diabetic neuropathy and the like.

Further, some of a series of indole derivatives having a thiazolidine ring or an oxazolidine ring as a partial structure, are known. For example, there is reported in Bioorg. Med. Chem. Lett., vol. 2(7), P705 (1992) that a series of 3-((4-oxo-2-thioxo-5-thiazolidinylidene)methyl)indole derivatives have cyclooxygenase and 5-lipoxygenase inhibitory activities. Arch. Pharm. (Weinheim)., vol. 304(7), P523 (1971) and European Patent No. 343643 disclose that a series of 2-((4-oxo-2-thioxo-5-thiazolidinylidene)methyl)indole derivatives have anti-inflammatory and anti-allergy activities. Japanese Examined Patent Publication No. 56175/1986 and European Laid Open Patent Publication No. 47109 disclose that a series of 3-((N-carboxymethyl-4-oxo-2-thioxo-5-thiazolidinylidene)methyl)indole derivatives have aldose-reductase inhibitory activities. Indian Drugs, vol. 22(10), P519 (1985) and J. Chem. Soc. Pak., vol. 4(1), P43 (1982) discloses a series of 3-((4-

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oxo-2-thioxo-5-thiazolidinyldene)methyl)indole derivatives have CNS activities. Japanese Unexamined Patent Publication No. 96941/1980 discloses that a series of 3-((4-oxo-2-thioxo-5-thiazolidinyldene)methyl)indole derivatives are useful as a photographic material of silver halide. Anal. Lett., vol. 17(A13), P1447 (1984) discloses that 3-((4-oxo-2-thioxo-5-thiazolidinyldene)methyl)indole is useful as a spectroscopic analytical reagent. J. Med. Chem., vol 21 (1), P82 (1977) discloses that a series of 3-(4-oxo-2-thioxo-5-thiazolidinylmethyl)indole derivatives have anti-bacterial activities. J. Med. Chem., vol. 10(5), P852 (1967) discloses that a series of 3-((4-oxo-2-thioxo-5-thiazolidinyldene)methyl)indole derivatives have decarboxylase inhibitory activities. However, it is not known at all that these compounds have a hypoglycemic effect.

Belgian Laid Open Patent Publication No. 889758 discloses that a compound having 2,4-dioxo-5-oxazolidinyl directly bonded with an indole ring as a hypoglycemic effect on rats. However, these compounds are not actually synthesized, and their effects are not clear. Also, US Patent No. 4,738,972 and PCT Publication No. 8607056 disclose that a compound having 2,4-dioxo-5-thiazolidinyl directly bonded to the 5-position of an indoline ring has a hypoglycemic effect on ob/ob mice. However, these compounds are not actually synthesized and

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their effects are not clear. European Laid Open Patent Publication No. 587377 discloses N-substituted 2- or 3-indolylmethylen-2-thioxo-4-thiazolidinone has a hypoglycemic effect on yellow obese diabetes mellitus mice, but its effect is not satisfactory.

On the other hand, aldose reductase (AR) is known to be an enzyme for reducing aldoses such as glucose and galactose to polyols such as sorbitol and galactitol in a living body. It is also known that accumulation of the polyols thus produced by the enzyme in organs induces or exacerbates various diabetic complications such as diabetic retinopathy, diabetic neuropathy and diabetic nephropathy, and therefore an inhibitor against this enzyme is useful as an agent for treating these diabetic complications.

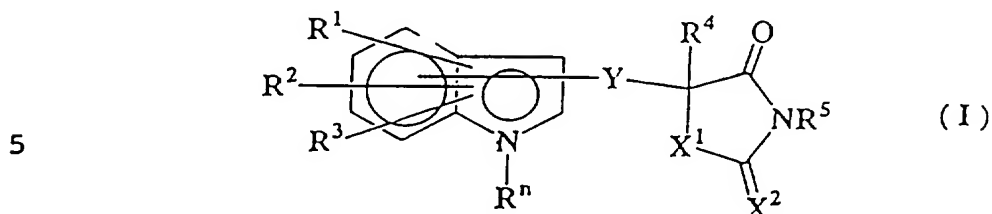
Under these circumstances, the present inventors have synthesized various thiazolidines which are not disclosed in the above-mentioned literatures, and have studied their properties. As this result, the present inventors have found compounds having excellent hypoglycemic effects and aldose-reductase inhibitory activities which were not exhibited by the above-mentioned known compounds. Thus, the present invention provides indole type thiazolidines capable of preventing or treating diabetes mellitus and diabetic complications.

DISCLOSURE OF THE INVENTION

The novel indole type thiazolidine derivatives of the

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present invention are indole type thiazolidines of the following formula (I) and their salts:



wherein X^1 is S or O;

X^2 is S, O or NH;

Y is CR^6R^7 (R^6 is a hydrogen atom, a C_1 - C_7 alkyl group or a C_3 - C_7 cycloalkyl group, and R^7 is a hydrogen atom, a C_1 - C_7 alkyl group or a C_3 - C_7 cycloalkyl group, or forms a bond together with R^4);

R^1 is a substituent at the 2-, 3-, 4-, 5-, 6- or 7-position of an indole ring, examples of which include a C_1 - C_{10} alkyl group, a C_2 - C_{10} alkenyl group, a C_2 - C_{10} alkynyl group, a C_1 - C_{10} alkoxy group, a C_2 - C_{10} alkenyloxy group, a C_1 - C_{10} alkylthio group, a C_1 - C_{10} monoalkylamino group or a di- C_1 - C_{10} alkylamino group (each of said C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_1 - C_{10} alkoxy, C_2 - C_{10} alkenyloxy, C_1 - C_{10} alkylthio, C_1 - C_{10} monoalkylamino and di- C_1 - C_{10} alkylamino groups may be substituted with a hydroxyl group or a C_1 - C_7 alkyl group), or

$-W_k-V_l-Z$ (Z is a C_3 - C_{10} cycloalkyl group, a C_3 - C_7 cycloalkenyl group, a C_6 - C_{14} aromatic group, a C_1 - C_{12} heterocyclic aromatic group (said heterocyclic aromatic group may contain at most 5 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and

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a nitrogen atom as constituents for the heterocyclic ring), or a C₁-C₆ heterocycloaliphatic group (said heterocycloaliphatic group may contain at most 3 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom as constituents for the heterocyclic ring) (each of said C₃-C₁₀ cycloalkyl, C₃-C₇ cycloalkenyl, C₆-C₁₄ aromatic, C₁-C₁₂ heterocyclic aromatic and C₁-C₆ heterocycloaliphatic groups may have at most 5 substituents selected from the group consisting of a hydrogen atom, a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group, a C₃-C₇ cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C₁-C₇ alkoxy group, a C₁-C₇ alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C₁-C₃ alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C₁-C₇-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group, a C₁-C₃ alkoxy group, a C₁-C₃ alkylthio group, a hydroxyl group, a halogen atom, a nitro group

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and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group and a thiazolidindion-5-yl methyl group),

5 V is O, S, SO, SO₂ or NR⁸ (R⁸ is a hydrogen atom or a C₁-C₃ alkyl group),

W is a divalent C₁-C₆ saturated or C₂-C₆ unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C₁-C₇ alkyl groups, and

10 each of k and ℓ is 0 or 1),

-V-W-Z (V, W and Z are as defined above),

-W-V-W-Z (V, W and Z are as defined above, and two W's may be the same or different), or

R¹ may be a hydrogen atom when Y is bonded at the 4-,
15 5-, 6- or 7-position of an indole ring,

each of R² and R³ is independently a hydrogen atom, a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group (said C₁-C₇ alkyl and C₃-C₇ cycloalkyl groups may be substituted with a hydroxyl group), a C₁-C₇ alkyloxy group, a benzyloxy
20 group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group, a pyrimidinyl group, a pyridazinyl group, a furanyl group, a thienyl group, a pyrrolyl group, a pyrazolyl group, an imidazolyl group, a pyranlyl group, a quinolyl group, a benzoxazolyl group, a
25 benzothiazolyl group or a benzimidazolyl group (each of said phenyl, naphthyl, benzyl, pyridyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, pyrazolyl,

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imidazolyl, pyranyl, quinolyl, benzoxazolyl,
benzothiazolyl and benzimidazolyl groups may be
substituted with at most 5 substituents selected from the
group consisting of a hydroxyl group, a C₁-C₇ alkyl
5 group, a C₁-C₇ alkoxy group and a halogen atom), a
hydroxyl group or halogen atom;

R⁴ is a hydrogen atom or a C₁-C₇ alkyl group, or
forms a bond together with R⁷;

R⁵ is a hydrogen atom or a carboxymethyl group; and

10 Rⁿ is a substituent at the 1-position of an indole
ring, examples of which include a hydrogen atom, a C₁-C₇
alkyl group, a C₃-C₇ cycloalkyl group, a C₁-C₄
alkoxymethyl group, an aryloxymethyl group, a C₁-C₄
alkylaminomethyl group, a substituted acetamidemethyl
15 group, a substituted thiomethyl group, a carboxyl group,
a C₁-C₇ acyl group, an arylcarbonyl group, a C₁-C₄
alkoxycarbonyl group, an aryloxy carbonyl group, a C₁-C₄
alkylaminocarbonyl group, an arylaminocarbonyl group, a
C₁-C₇ alkoxy group, a C₁-C₇ alkoxyalkyloxy group, a
20 trialkylsilyl group, a trialkylarylsilyl group, an
alkylsulfonyl group or an arylsulfonyl group.

The substituents of the compound of the formula (I)
of the present invention will be explained with reference
to typical examples, but it should be understood that the
25 scope of the present invention is by no means limited by
these examples.

Each substituent in the formula (I) will be

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specifically described hereinafter.

In the definition of R^1 :

R^1 is a substituent at the 2-, 3-, 4-, 5-, 6- or 7-position, preferably at the 2- or 5-position of an indole
5 ring.

The C_1 - C_{10} alkyl group includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, 1-pentyl, 2-pentyl, 3-pentyl, i-pentyl, neo-pentyl, t-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-methyl-1-ethyl-n-pentyl, 1,1,2-trimethyl-n-propyl, 1,2,2-trimethyl-n-propyl, 3,3-dimethyl-n-butyl, 1-heptyl, 2-heptyl, 1-ethyl-1,2-dimethyl-n-propyl, 1-ethyl-2,2-dimethyl-n-propyl, 1-octyl, 3-octyl, 4-methyl-3-n-heptyl, 6-methyl-2-n-heptyl, 2-propyl-1-n-heptyl, 2,4,4-trimethyl-1-n-pentyl, 1-nonyl, 2-nonyl, 2,6-dimethyl-4-n-heptyl, 3-ethyl-2,2-dimethyl-3-n-pentyl, 3,5,5-trimethyl-1-n-hexyl, 1-decyl, 2-decyl, 4-decyl, 3,7-dimethyl-1-n-octyl, and 3,7-dimethyl-3-n-octyl. Preferred is a C_4 - C_{10} alkyl group which includes, for example, n-butyl, i-butyl, s-butyl, t-butyl, 1-pentyl, 2-pentyl, 3-pentyl, i-pentyl, neo-pentyl, t-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-methyl-1-ethyl-n-pentyl, 1,1,2-trimethyl-n-propyl, 1,2,2-trimethyl-n-propyl, 3,3-dimethyl-n-butyl, 1-heptyl, 2-heptyl, 1-ethyl-1,2-dimethyl-n-propyl, 1-ethyl-2,2-dimethyl-n-propyl, 1-octyl, 3-octyl, 4-methyl-3-n-heptyl, 6-methyl-2-n-heptyl, 2-propyl-1-n-heptyl, 2,4,4-trimethyl-1-n-pentyl, 1-nonyl, 2-nonyl, 2,6-dimethyl-4-n-

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heptyl, 3-ethyl-2,2-dimethyl-3-n-pentyl, 3,5,5-trimethyl-1-n-hexyl, 1-decyl, 2-decyl, 4-decyl, 3,7-dimethyl-1-n-octyl and 3,7-dimethyl-3-n-octyl. Each group may be substituted by a hydroxyl group or a C₁-C₇ alkyl group.

5 The C₂-C₁₀ alkenyl group includes, for example, ethenyl, 1-propenyl, 2-propenyl, 1-methylvinyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-methyl-1-propenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 1-ethyl-2-vinyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1,2-
10 dimethyl-1-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-1-propenyl, 1-ethyl-2-propenyl, 1-methyl-1-butenyl, 1-methyl-2-butenyl, 2-methyl-1-butenyl, 1-i-propylvinyl, 2,4-pentadienyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2,4-hexadienyl, 1-methyl-1-pentenyl,
15 1-heptenyl, 1-octenyl, 1-nonenyl and 1-decenyl.

Preferred is a C₅-C₁₀ alkenyl group which includes, for example, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1,2-dimethyl-1-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-1-propenyl, 1-ethyl-2-propenyl, 1-methyl-1-butenyl,
20 1-methyl-2-butenyl, 2-methyl-1-butenyl, 1-i-propylvinyl, 2,4-pentadienyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2,4-hexadienyl, 1-methyl-1-pentenyl, 1-heptenyl, 1-octenyl, 1-nonenyl and 1-decenyl. Each group may be substituted by a hydroxyl group or a C₁-C₇
25 alkyl group.

The C₂-C₁₀ alkynyl group includes, for example, ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-

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butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-heptynyl, 1-octynyl, 1-nonynyl, and 1-decynyl. Preferred is a C₅-C₁₀ alkynyl group which includes, for example, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-heptynyl, 1-octynyl, 1-nonynyl and 1-decynyl. Each group may be substituted by a hydroxyl group or a C₁-C₇ alkyl group.

The C₁-C₁₀ alkoxy group includes, for example, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy and decyloxy. Preferred is a C₄-C₁₀ alkoxy group which includes, for example, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy and decyloxy. Each group may be substituted by a hydroxyl group or a C₁-C₇ alkyl group.

The C₂-C₁₀ alkenyloxy group includes, for example, ethenyloxy, 1-propenyloxy, 2-propenyloxy, 1-butenyloxy, 2-butenyloxy, 3-butenyloxy, 1-pentenyloxy, 2-pentenyloxy, 3-pentenyloxy, 4-pentenyloxy, 2,4-pentadienyloxy, 1-hexenyloxy, 2-hexenyloxy, 3-hexenyloxy, 4-hexenyloxy, 5-hexenyloxy, 2,4-hexadienyloxy, 1-heptenyloxy, 1-octenyloxy, 1-nonenyloxy and 1-decenyloxy. Preferred is a C₅-C₁₀ alkenyloxy which includes, for example, 1-pentenyloxy, 2-pentenyloxy, 3-pentenyloxy, 4-pentenyloxy, 2,4-pentadienyloxy, 1-hexenyloxy, 2-hexenyloxy, 3-

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hexenyloxy, 4-hexenyloxy, 5-hexenyloxy, 2,4-hexadienyloxy, 1-heptenyloxy, 1-octenyloxy, 1-nonyenyloxy and 1-decenyloxy. Each group may be substituted by a hydroxyl group or a C₁-C₇ alkyl group.

5 The C₁-C₁₀ alkylthio group includes, for example, methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, i-butylthio, s-butylthio, t-butylthio, pentylthio, hexylthio, heptylthio, octylthio, nonylthio and decylthio. Preferred is a C₅-C₁₀ alkylthio which
10 includes, for example, pentylthio, hexylthio, heptylthio, octylthio, nonylthio and decylthio. Each group may be substituted by a hydroxyl group or a C₁-C₇ alkyl group.

 The C₁-C₁₀ monoalkylamino group includes, for example, methylamino, ethylamino, n-propylamino, i-
15 propylamino, n-butylamino, i-butylamino, s-butylamino, t-butylamino, pentylamino, hexylamino, heptylamino, octylamino, nonylamino and decylamino. Preferred is a C₅-C₁₀ monoalkylamino group which includes, for example, pentylamino, hexylamino, heptylamino, octylamino,
20 nonylamino and decylamino. Each group may be substituted by a hydroxyl group or a C₁-C₇ alkyl group.

 The di-C₁-C₁₀ alkylamino group includes, for example, dimethylamino, diethylamino, di-n-propylamino, di-i-propylamino, d-n-hexylamino, N-methyl-N-n-pentylamino, N-
25 methyl-N-n-hexylamino, N-methyl-N-n-heptylamino, N-methyl-N-n-octylamino, N-methyl-N-n-nonylamino, and N-methyl-N-n-decylamino. Preferred are, for example, N-

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methyl-N-n-pentylamino, N-methyl-N-n-hexylamino, N-methyl-N-n-heptylamino, N-methyl-N-n-octylamino, N-methyl-N-n-nonylamino, and N-methyl-N-n-decylamino. Each group may be substituted by a hydroxyl group or a C₁-C₇ alkyl group.

In the definition of Z:

The C₃-C₁₀ cycloalkyl group includes, for example, cyclopropyl, 1-methyl-cyclopropyl, 2-methyl-cyclopropyl, 4-methyl-cyclohexyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, 1-adamantyl, and 2-adamantyl. Preferred is a C₆-C₁₀ cycloalkyl group which includes, for example, cyclohexyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, 1-adamantyl and 2-adamantyl. Each group may have at most 5 substituents (the substituents may, for example, be a hydrogen atom, a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group, a C₃-C₇ cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C₁-C₇ alkoxy group, a C₁-C₇ alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C₁-C₃ alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy

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group, a tri-C₁-C₇-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted
5 with at most 5 substituents selected from the group consisting of a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group, a C₁-C₃ alkoxy group, a C₁-C₃ alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-
10 tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group).

The C₃-C₇ cycloalkenyl group includes, for example, cyclohexenyl (said cyclohexenyl includes 1-cyclohexenyl,
15 2-cyclohexenyl, and 3-cyclohexenyl), cyclopentadienyl, 2-bicyclo[2.2.1]heptenyl, and 2,5-bicyclo[2.2.1]heptadienyl. Each group may have at most 5 substituents (said substituents may, for example, be a hydrogen atom, a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl
20 group, a C₃-C₇ cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C₁-C₇ alkoxy group, a C₁-C₇ alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a
25 methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C₁-C₃ alkoxycarbonyl group, a nitrile group, a carbamoyl

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group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C₁-C₇-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, 5 imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group, a C₁-C₃ alkoxy group, a C₁-C₃ alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a 10 dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group).

The C₆-C₁₄ aromatic group includes, for example, 15 phenyl, naphthyl (said naphthyl includes α -naphthyl, and β -naphthyl), indenyl (said indenyl includes 1-indenyl, 2-indenyl, 3-indenyl, 4-indenyl, 5-indenyl, 6-indenyl, and 7-indenyl), indanyl (said indanyl includes 1-indanyl, 2-indanyl, 4-indanyl, and 5-indanyl), and fluorenyl (said 20 fluorenyl includes 1-fluorenyl, 2-fluorenyl, 3-fluorenyl, 4-fluorenyl, and 9-fluorenyl). Preferred is a C₆-C₁₄ aromatic group which includes, for example, phenyl, naphthyl (said naphthyl includes α -naphthyl, and β -naphthyl), and fluorenyl (said fluorenyl includes 1- 25 fluorenyl, 2-fluorenyl, 3-fluorenyl, 4-fluorenyl, and 9-fluorenyl). Each group may have at most 5 substituents (said substituents may, for example, be a hydrogen atom,

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a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group, a C₃-C₇ cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C₁-C₇ alkoxy group, a C₁-C₇ alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C₁-C₃ alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C₁-C₇-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group, a C₁-C₃ alkoxy group, a C₁-C₃ alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group).

The C₁-C₁₂ heterocyclic aromatic group is a heterocyclic group having a 5-15 membered monocyclic or condensed ring containing at most 5 hetero-atoms in the ring, selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom. Examples of the

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heterocyclic aromatic group include furyl (said furyl includes 2-furyl, and 3-furyl), thienyl (said thienyl includes 2-thienyl, and 3-thienyl), pyrrolyl (said pyrrolyl includes 1-pyrrolyl, 2-pyrrolyl, and 3-pyrrolyl), oxazolyl (said oxazolyl includes 2-oxazolyl, 4-oxazolyl, and 5-oxazolyl), thiazolyl (said thiazolyl includes 2-thiazolyl, 4-thiazolyl, and 5-thiazolyl), isoxazolyl (said isoxazolyl includes 3-isoxazolyl, 4-isoxazolyl, and 5-isoxazolyl), isothiazolyl (said isothiazolyl includes 3-isothiazolyl, 4-isothiazolyl, and 5-isothiazolyl), furazanyl (said furazanyl includes 3-furazanyl), pyrazolyl (said pyrazolyl includes 1-pyrazolyl, 3-pyrazolyl, and 4-pyrazolyl), oxopyrazolyl (said oxopyrazolyl includes 3-oxopyrazol-1-yl, 3-oxopyrazol-2-yl, 3-oxopyrazol-3-yl, 3-oxopyrazol-4-yl, and 4-oxopyrazol-3-yl), imidazolyl (said imidazolyl includes 1-imidazolyl, 2-imidazolyl, and 4-imidazolyl), oxoimidazolyl (said oxoimidazolyl includes 2-oxoimidazol-1-yl, and 2-oxoimidazol-4-yl), triazolyl (said triazolyl includes 1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl, 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, and 1,2,4-triazol-4-yl), triazolonyl (said triazolonyl includes 1,2,4(2H,4H)-triazol-3-on-2-yl, 1,2,4-(2H,4H)-triazol-3-on-4-yl, 1,2,4(2H,4H)-triazol-3-on-5-yl, 1,2,4(1H,2H)-triazol-3-on-1-yl, 1,2,4(1H,2H)-triazol-3-on-2-yl, and 1,2,4(1H,2H)-triazol-3-on-5-yl), tetrazolyl (said tetrazolyl includes 1-tetrazolyl, 2-tetrazolyl, and

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5-tetrazolyl), pyranyl (said pyranyl includes 2-pyranyl, 3-pyranyl, and 4-pyranyl), pyridyl (said pyridyl includes 2-pyridyl, 3-pyridyl, and 4-pyridyl), pyridonyl (said pyridonyl includes 2-pyridon-1-yl, 2-pyridon-3-yl, 2-
5 pyridon-4-yl, 2-pyridon-5-yl, 2-pyridon-6-yl, 4-pyridon-1-yl, 4-pyridon-2-yl, and 4-pyridon-3-yl), pyridazinyl (said pyridazinyl includes 3-pyridazinyl, and 4-pyridazinyl), pyridazinonyl (said pyridazinonyl includes 3(2H)-pyridazinon-2-yl, 3(2H)-pyridazinon-4-yl, 3(2H)-
10 pyridazinon-5-yl, 3(2H)-pyridazinon-6-yl, 4(1H)-pyridazinon-1-yl, 4(1H)-pyridazinon-3-yl, 4(1H)-pyridazinon-5-yl, and 4(1H)-pyridazinon-6-yl), pyrimidinyl (said pyrimidinyl includes 2-pyrimidinyl, 4-pyrimidinyl, and 5-pyrimidinyl), pyrimidinonyl (said
15 pyrimidinonyl includes (2(1H)-pyrimidinon-1-yl, 2(1H)-pyrimidinon-4-yl, 2(1H)-pyrimidinon-5-yl, 2(1H)-pyrimidinon-6-yl, 4(3H)-pyrimidinon-2-yl, 4(3H)-pyrimidinon-3-yl, 4(3H)-pyrimidinon-5-yl, 4(3H)-pyrimidinon-6-yl, 4(1H)-pyrimidinon-1-yl, 4(1H)-
20 pyrimidinon-2-yl, 4(1H)-pyrimidinon-5-yl, and 4(1H)-pyrimidinon-6-yl), pyrazinyl (said pyrazinyl includes 2-pyrazinyl, 2(1H)-pyrazin-1-yl, 2(1H)-pyrazin-3-yl, 2(1H)-pyrazin-5-yl, and 2(1H)-pyrazin-6-yl), triazinyl (said triazinyl includes 1,2,3-triazin-4-yl, 1,2,3-triazin-5-
25 yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, and 1,2,4-triazin-6-yl), tetrazinyl (said tetrazinyl includes 1,2,3,4-tetrazin-5-yl, and 1,2,4,5-tetrazin-3-yl),

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indolyl (said indolyl includes 1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, and 7-indolyl), quinolyl (said quinolyl includes 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, and 8-quinolyl), quinolonyl (said quinolonyl includes 2-quinolon-1-yl, 2-quinolon-3-yl, 2-quinolon-4-yl, 2-quinolon-5-yl, 2-quinolon-6-yl, 2-quinolon-7-yl, 2-quinolon-8-yl, 4-quinolon-1-yl, 4-quinolon-2-yl, 4-quinolon-3-yl, 4-quinolon-5-yl, 4-quinolon-6-yl, 4-quinolon-7-yl, and 4-quinolon-8-yl), benzofuranyl (said benzofuranyl includes 2-benzofuranyl, 3-benzofuranyl, 4-benzofuranyl, 5-benzofuranyl, 6-benzofuranyl, and 7-benzofuranyl), benzothienyl (said benzothienyl includes 2-benzothienyl, 3-benzothienyl, 4-benzothienyl, 5-benzothienyl, 6-benzothienyl, and 7-benzothienyl), isoquinolyl (said isoquinolyl includes 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, and 8-isoquinolyl), isoquinolonyl (said isoquinolonyl includes 1-isoquinolon-2-yl, 1-isoquinolon-3-yl, 1-isoquinolon-4-yl, 1-isoquinolon-5-yl, 1-isoquinolon-6-yl, 1-isoquinolon-7-yl, 1-isoquinolon-8-yl, 3-isoquinolon-2-yl, 3-isoquinolon-4-yl, 3-isoquinolon-5-yl, 3-isoquinolon-6-yl, 3-isoquinolon-7-yl, and 3-isoquinolon-8-yl), benzoxazolyl (said benzoxazolyl includes 2-benzoxazolyl, 4-benzoxazolyl, 5-benzoxazolyl, 6-benzoxazolyl, and 7-benzoxazolyl), benzothiazolyl (said benzothiazolyl includes 2-benzothiazolyl, 4-

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benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, and 7-benzothiazolyl), benzopyrazolyl (said benzopyrazolyl includes 1-benzopyrazolyl, 2-benzopyrazolyl, 3-benzopyrazolyl, 4-benzopyrazolyl, 5-benzopyrazolyl, 6-benzopyrazolyl, and 7-benzopyrazolyl), benzimidazolyl (said benzimidazolyl includes 1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, and 5-benzimidazolyl), benzotriazolyl (said benzotriazolyl includes 1-benzotriazolyl, 4-benzotriazolyl, and 5-benzotriazolyl), benzopyranyl (said benzopyranyl includes 2-benzopyranyl, 3-benzopyranyl, 4-benzopyranyl, 5-benzopyranyl, 6-benzopyranyl, 7-benzopyranyl, and 8-benzopyranyl), indolizinylyl (said indolizinylyl includes 1-indolizinylyl, 2-indolizinylyl, 3-indolizinylyl, 5-indolizinylyl, 6-indolizinylyl, 7-indolizinylyl, and 8-indolizinylyl), purinylyl (said purinylyl includes 2-purinylyl, 6-purinylyl, 7-purinylyl, and 8-purinylyl), phthalazinylyl (said phthalazinylyl includes 1-phthalazinylyl, 5-phthalazinylyl, and 6-phthalazinylyl), oxophthalazinylyl (said oxophthalazinylyl includes 1-oxophthalazin-2-yl, 1-oxophthalazin-4-yl, 1-oxophthalazin-5-yl, 1-oxophthalazin-6-yl, 1-oxophthalazin-7-yl, and 1-oxophthalazin-8-yl), naphthyridinylyl (said naphthyridinylyl includes 2-naphthyridinylyl, 3-naphthyridinylyl, and 4-naphthyridinylyl), quinoxalinylyl (said quinoxalinylyl includes 2-quinoxalinylyl, 5-quinoxalinylyl, and 6-quinoxalinylyl), quinazolinylyl (said quinazolinylyl includes 2-quinazolinylyl, 4-quinazolinylyl, 5-quinazolinylyl, 6-quinazolinylyl, 7-

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quinazolinyl, and 8-quinazolinyl), cinnolinyl (said cinnolinyl includes 3-cinnolinyl, 4-cinnolinyl, 5-cinnolinyl, 6-cinnolinyl, 7-cinnolinyl, and 8-cinnolinyl), benzodioxolyl (said benzodioxolyl includes 1,3-benzodioxol-4-yl, and 1,3-benzodioxol-5-yl), benzodioxanyl (said benzodioxanyl includes 1,4-benzodioxan-2-yl, 1,4-benzodioxan-5-yl, and 1,4-benzodioxan-6-yl), oxonaphthalenyl (said oxonaphthalenyl includes 1,4-oxonaphthalen-2-yl, 1,4-oxonaphthalen-5-yl, and 1,4-oxonaphthalen-6-yl), 2,3-dihydrobenzofuranyl (said 2,3-dihydrobenzofuranyl includes 2,3-dihydro-4-benzofuranyl, 2,3-dihydro-5-benzofuranyl, 2,3-dihydro-6-benzofuranyl, and 2,3-dihydro-7-benzofuranyl), benzothiazinyl (said benzothiazinyl includes 1,4-benzothiazin-2-yl, 1,4-benzothiazin-3-yl, 1,4-benzothiazin-4-yl, 1,4-benzothiazin-5-yl, 1,4-benzothiazin-6-yl, 1,4-benzothiazin-7-yl, and 1,4-benzothiazin-8-yl), pteridinyl (said pteridinyl includes 2-pteridinyl, 4-pteridinyl, 6-pteridinyl, and 7-pteridinyl), pyrazolo[1,5-a]pyrimidinyl (said pyrazolo[1,5-a]pyrimidinyl includes pyrazolo[1,5-a]pyrimidin-2-yl, pyrazolo[1,5-a]pyrimidin-3-yl, pyrazolo[1,5-a]pyrimidin-5-yl, pyrazolo[1,5-a]pyrimidin-6-yl, and pyrazolo[1,5-a]pyrimidin-7-yl), pyrazolo[5,1-c][1,2,4]triazinyl (said pyrazolo[5,1-c][1,2,4]triazinyl includes pyrazolo[5,1-c][1,2,4]triazin-3-yl, pyrazolo[5,1-c][1,2,4]triazin-4-yl, pyrazolo[5,1-

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c][1,2,4]triazin-7-yl, and pyrazolo[5,1-c][1,2,4]triazin-8-yl), thiazolo[3,2-b]triazolyl (said thiazolo[3,2-b]triazolyl includes thiazolo[3,2-b]triazol-2-yl, thiazolo[3,2-b]triazol-5-yl, and thiazolo[3,2-b]triazol-6-yl), benzopyrano[2,3-b]pyridyl (said benzopyrano[2,3-b]pyridyl includes benzopyrano[2,3-b]pyridin-2-yl, benzopyrano[2,3-b]pyridin-3-yl, benzopyrano[2,3-b]pyridin-4-yl, benzopyrano[2,3-b]pyridin-5-yl, benzopyrano[2,3-b]pyridin-6-yl, benzopyrano[2,3-b]pyridin-7-yl, benzopyrano[2,3-b]pyridin-8-yl, and benzopyrano[2,3-b]pyridin-9-yl), 5H-benzopyrano[2,3-b]pyridonyl (said 5H-benzopyrano[2,3-b]pyridonyl includes 5H-benzopyrano[2,3-b]pyridin-5-on-2-yl, 5H-benzopyrano[2,3-b]pyridin-5-on-3-yl, 5H-benzopyrano[2,3-b]pyridin-5-on-4-yl, 5H-benzopyrano[2,3-b]pyridin-5-on-6-yl, 5H-benzopyrano[2,3-b]pyridin-5-on-7-yl, and 5H-benzopyrano[2,3-b]pyridin-5-on-8-yl), xanthenyl (said xanthenyl includes 1-xanthenyl, 2-xanthenyl, 3-xanthenyl, 4-xanthenyl, and 9-xanthenyl), phenoxathiinyl (said phenoxathiinyl includes 1-phenoxathiinyl, 2-phenoxathiinyl, 3-phenoxathiinyl, and 4-phenoxathiinyl), carbazolyl (said carbazolyl includes 1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl, and 9-carbazolyl), acridinyl (said acridinyl includes 1-acridinyl, 2-acridinyl, 3-acridinyl, 4-acridinyl, and 9-acridinyl), phenazinyl (said phenazinyl includes 1-phenazinyl, 2-phenazinyl, 3-phenazinyl, and 4-

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phenazinyl), phenothiazinyl (said phenothiazinyl includes 1-phenothiazinyl, 2-phenothiazinyl, 3-phenothiazinyl, 4-phenothiazinyl, and 10-phenothiazinyl), phenoxazinyl (said phenoxazinyl includes 1-phenoxazinyl, 2-phenoxazinyl, 3-phenoxazinyl, 4-phenoxazinyl, and 10-phenoxazinyl), and thianthrenyl (said thianthrenyl includes 1-thianthrenyl, 2-thianthrenyl, 3-thianthrenyl, 4-thianthrenyl, 6-thianthrenyl, 7-thianthrenyl, 8-thianthrenyl, and 9-thianthrenyl). Preferred examples of the C₁-C₁₂ heterocyclic aromatic group include furyl (said furyl includes 2-furyl, and 3-furyl), thienyl (said thienyl includes 2-thienyl, and 3-thienyl), pyrrolyl (said pyrrolyl includes 1-pyrrolyl, 2-pyrrolyl, and 3-pyrrolyl), oxazolyl (said oxazolyl includes 2-oxazolyl, 4-oxazolyl, and 5-oxazolyl), thiazolyl (said thiazolyl includes 2-thiazolyl, 4-thiazolyl, and 5-thiazolyl), isoxazolyl (said isoxazolyl includes 3-isoxazolyl, 4-isoxazolyl, and 5-isoxazolyl), isothiazolyl (said isothiazolyl includes 3-isothiazolyl, 4-isothiazolyl, and 5-isothiazolyl), imidazolyl (said imidazolyl includes 1-imidazolyl, 2-imidazolyl, and 4-imidazolyl), pyridyl (said pyridyl includes 2-pyridyl, 3-pyridyl, and 4-pyridyl), pyridazinyl (said pyridazinyl includes 3-pyridazinyl, and 4-pyridazinyl), pyridazinonyl (said pyridazinonyl includes 3(2H)-pyridazinon-2-yl, 3(2H)-pyridazinon-4-yl, 3(2H)-pyridazinon-5-yl, and 3(2H)-pyridazinon-6-yl), pyrimidinyl (said pyrimidinyl includes

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2-pyrimidinyl, 4-pyrimidinyl, and 5-pyrimidinyl),
pyrazinyl (said pyrazinyl includes 2-pyrazinyl), indolyl
(said indolyl includes 1-indolyl, 2-indolyl, 3-indolyl,
4-indolyl, 5-indolyl, 6-indolyl, and 7-indolyl), quinolyl
5 (said quinolyl includes 2-quinolyl, 3-quinolyl, 4-
quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, and 8-
quinolyl), benzoxazolyl (said benzoxazolyl includes 2-
benzoxazolyl, 4-benzoxazolyl, 5-benzoxazolyl, 6-
benzoxazolyl, and 7-benzoxazolyl), benzothiazolyl (said
10 benzothiazolyl includes 2-benzothiazolyl, 4-
benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, and
7-benzothiazolyl), benzimidazolyl (said benzimidazolyl
includes 1-benzimidazolyl, 2-benzimidazolyl, 4-
benzimidazolyl, and 5-benzimidazolyl), phthalazinyl (said
15 phthalazinyl includes 1-phthalazinyl, 5-phthalazinyl, and
6-phthalazinyl), quinoxalinyl (said quinoxalinyl includes
2-quinoxalinyl, 5-quinoxalinyl, and 6-quinoxalinyl),
benzodioxolyl (said benzodioxolyl includes 1,3-
benzodioxol-4-yl, and 1,3-benzodioxol-5-yl),
20 benzothiazinyl (said benzothiazinyl includes 1,4-
benzothiazin-2-yl, 1,4-benzothiazin-3-yl, 1,4-
benzothiazin-4-yl, 1,4-benzothiazin-5-yl, 1,4-
benzothiazin-6-yl, 1,4-benzothiazin-7-yl, and 1,4-
benzothiazin-8-yl), pyrazolo[1,5-a]pyrimidinyl (said
25 pyrazolo[1,5-a]pyrimidinyl includes pyrazolo[1,5-
a]pyrimidin-2-yl, pyrazolo[1,5-a]pyrimidin-3-yl,
pyrazolo[1,5-a]pyrimidin-5-yl, pyrazolo[1,5-a]pyrimidin-

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6-yl, and pyrazolo[1,5-a]pyrimidin-7-yl), pyrazolo[5,1-c][1,2,4]triazinyl (said pyrazolo[5,1-c][1,2,4]triazinyl includes pyrazolo[5,1-c][1,2,4]triazin-3-yl, pyrazolo[5,1-c][1,2,4]triazin-4-yl, pyrazolo[5,1-c][1,2,4]triazin-7-yl, and pyrazolo[5,1-c][1,2,4]triazin-8-yl), thiazolo[3,2-b]triazolyl (said thiazolo[3,2-b]triazolyl includes thiazolo[3,2-b]triazol-2-yl, thiazolo[3,2-b]triazol-5-yl, and thiazolo[3,2-b]triazol-6-yl), and benzopyrano[2,3-b]pyridyl (said benzopyrano[2,3-b]pyridyl includes benzopyrano[2,3-b]pyridin-2-yl, benzopyrano[2,3-b]pyridin-3-yl, benzopyrano[2,3-b]pyridin-4-yl, benzopyrano[2,3-b]pyridin-5-yl, benzopyrano[2,3-b]pyridin-6-yl, benzopyrano[2,3-b]pyridin-7-yl, benzopyrano[2,3-b]pyridin-8-yl, and benzopyrano[2,3-b]pyridin-9-yl). Each group may have at most 5 substituents (said substituents may, for example, be a hydrogen atom, a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group, a C₃-C₇ cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C₁-C₇ alkoxy group, a C₁-C₇ alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C₁-C₃ alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a

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tri-C₁-C₇-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted
5 with at most 5 substituents selected from the group consisting of a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group, a C₁-C₃ alkoxy group, a C₁-C₃ alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-
10 tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group).

The C₁-C₆ heterocycloaliphatic group is a heterocyclic group having a 3-8 membered monocyclic or
15 condensed dicyclic ring containing at most 3 hetero-atoms in the ring, selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom. Examples of the heterocycloaliphatic group include piperidyl (said piperidyl includes 1-piperidyl, 2-piperidyl, 3-piperidyl,
20 and 4-piperidyl), pyrrolidinyl (said pyrrolidinyl includes 1-pyrrolidinyl, 2-pyrrolidinyl, and 3-pyrrolidinyl), imidazolidinyl (said imidazolidinyl includes 1-imidazolidinyl, 2-imidazolidinyl, and 4-imidazolidinyl), pyrazolidinyl (said pyrazolidinyl
25 includes 1-pyrazolidinyl, 3-pyrazolidinyl, and 4-pyrazolidinyl), morpholinyl (said morpholinyl includes 2-morpholinyl, 3-morpholinyl, and 4-morpholinyl), and

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tetrahydrofuranyl (said tetrahydrofuranyl includes 2-tetrahydrofuranyl, and 3-tetrahydrofuranyl). Each group may have at most 5 substituents (said substituents may, for example, be a hydrogen atom, a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group, a C₃-C₇ cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C₁-C₇ alkoxy group, a C₁-C₇ alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C₁-C₃ alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C₁-C₇-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group, a C₁-C₃ alkoxy group, a C₁-C₃ alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group).

In the definitions of R^a, R^b and R^c:

The C₁-C₇ alkyl group includes, for example, methyl,

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ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl, and n-heptyl. Preferred are methyl, ethyl and n-propyl. Each group may be substituted with a hydroxyl group.

5 The C₃-C₇ cycloalkyl group includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]heptyl, and bicyclo[3.1.1]heptyl. Preferred are cyclopropyl and cyclohexyl. Each group may be substituted by a hydroxyl
10 group.

 The C₃-C₇ cycloalkenyl group includes, for example, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, cyclopentadienyl, 2-bicyclo[2.2.1]heptenyl and 2,5-bicyclo[2.2.1]heptadienyl. Each group may be substituted
15 by a hydroxyl group.

 The C₁-C₇ alkoxy group includes, for example, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentyloxy, hexyloxy and heptyloxy.

20 The C₁-C₇ alkylthio group includes, for example, methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, i-butylthio, s-buthylthio, t-butylthio, pentylthio, hexylthio and heptylthio.

 The tri-C₁-C₇-alkylsilyloxy group includes, for
25 example, trimethylsilyloxy, triethylsilyloxy, triisopropylsilyloxy, diethylisopropylsilyloxy, dimethylisopropylsilyloxy, di-t-butylmethylsilyloxy,

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isopropyldimethylsilyloxy, t-butyldimethylsilyloxy, thexyldimethylsilyloxy or the like, preferably t-butyldimethylsilyloxy or the like.

The naphthyl group includes an α -naphthyl group, a β -
5 naphthyl group. The furanyl group includes a 2-furanyl group and a 3-furanyl group. The thienyl group includes a 2-thienyl group and a 3-thienyl group. The imidazolyl group includes a 1-imidazolyl group, a 2-imidazolyl group and a 4-imidazolyl group. The pyridyl group includes a
10 2-pyridyl group and a 3-pyridyl group and a 4-pyridyl group. Each groups may be substituted with at most 5 substituents selected from the group consisting of a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group, a C_1 - C_3 alkoxy group, a C_1 - C_3 alkylthio group, a hydroxyl group, a
15 fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group.

The phenyl and the benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl
20 group, a C_1 - C_3 alkoxy group, a C_1 - C_3 alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group.

The C_1 - C_3 alkoxycarbonyl group includes, for example, methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl and i-
25 propoxycarbonyl.

The halogen atom includes a fluorine atom, a chlorine atom, a bromine atom and an iodine atom. Preferred are a

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fluorine atom, a chlorine atom and a bromine atom.

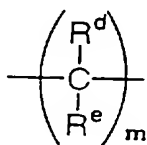
V is O, S, SO, SO₂ or NR⁸ (R⁸ is a hydrogen atom or C₁-C₃ alkyl (which may, for example, be methyl, ethyl, n-propyl or i-propyl, preferably methyl)). It is
 5 preferably S, SO, SO₂ or NR⁸.

W is a divalent C₁-C₆ saturated or C₂-C₆ unsaturated hydrocarbon group which may be substituted with at most 3, preferably at most 2, of hydroxyl, oxo and C₁-C₇ alkyl groups.

10 The C₁-C₇ alkyl group includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl and n-heptyl. Preferred may, for example, be methyl.

W is preferably

15



wherein m is from 1 to 5, and each of R^d and R^e is a hydrogen atom, a methyl group or a hydroxyl group, or R^d
 20 and R^e together form an oxo group, or adjacent R^d's together form a double bond, or adjacent R^d's and R^e's together form a triple bond (provided that R^d and R^e on the first carbon atom adjacent to N are not hydroxyl groups and provided that R^d and R^e on the first carbon
 25 atom adjacent to O are not hydroxyl groups or do not together form an oxo group).

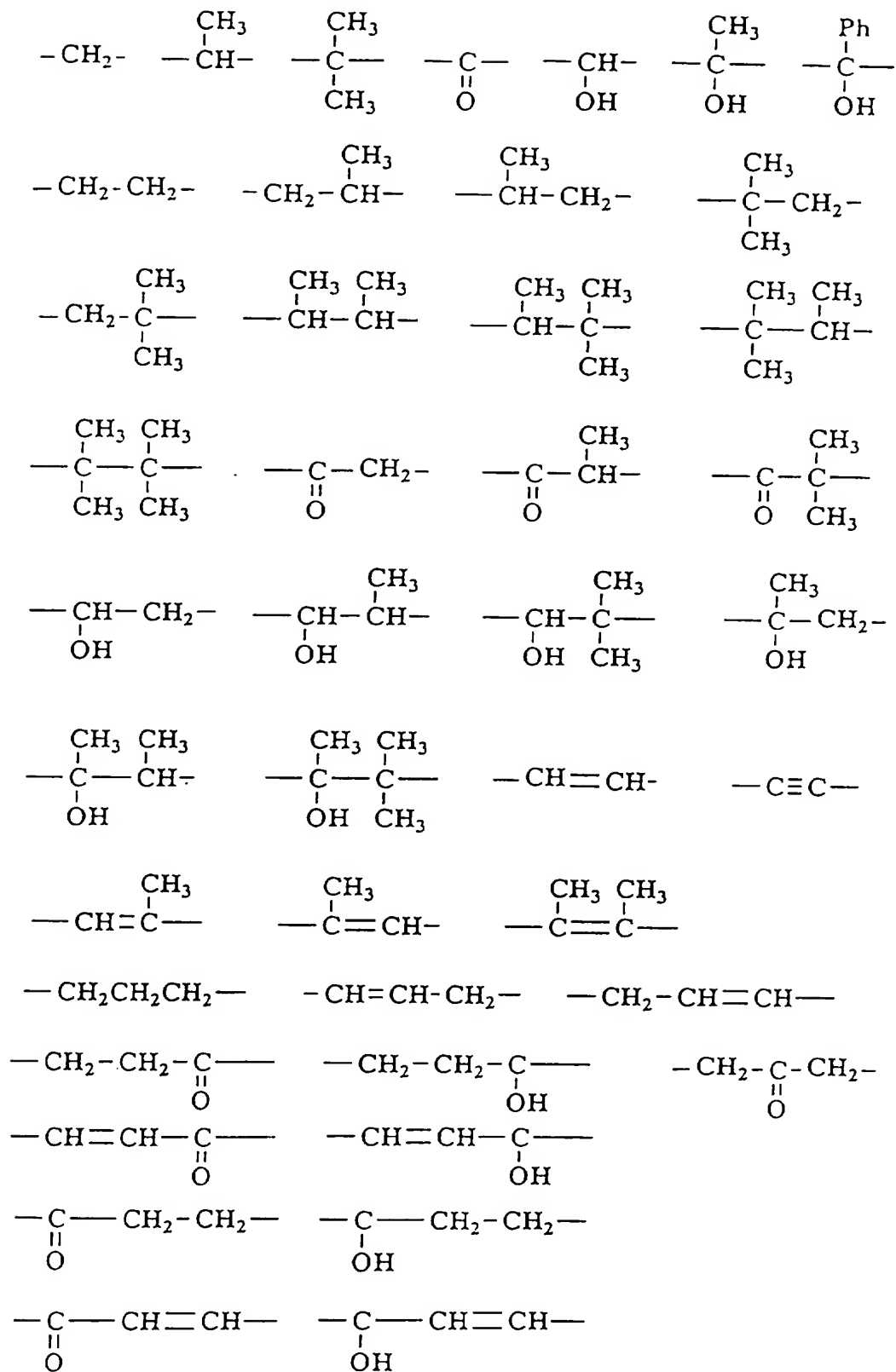
R¹ may be -W_x-V_z-Z, -V-W-Z or -W-V-W-Z in addition to

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the one mentioned above.

$-W_k-V_l-Z$ may, for example, be $-W-Z$, $-V-Z$ or $-W-V-Z$.

Preferable examples of $-W-$ in the above $-W-Z$ are illustrated below.



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Also, preferable examples of -V- in the above -V-Z include S, SO and SO₂.

Also, preferable examples of -W-V- in the above -W-V-Z include -CO-NR⁸- (R⁸ is a hydrogen atom or a C₁-C₃ alkyl group (e.g. methyl, ethyl, n-propyl or i-propyl, preferably methyl)).

Also, preferable examples of -V-W- in the above -V-W-Z include -O-(CH₂)_n- (n is from 1 to 5).

Also, preferable examples of -W-V-W- in the above -W-V-W-Z include -(CH₂)_n-NR⁸-CO- (n is from 1 to 5, R⁸ is a hydrogen atom or a C₁-C₃ alkyl group (e.g. methyl, ethyl, n-propyl or i-propyl, preferably methyl)).

Each of R² and R³ independently is a hydrogen atom, a C₁-C₇ alkyl group (which may, for example, be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl or n-heptyl, preferably methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl, and said C₁-C₇ alkyl group may be substituted with at most two hydroxyl groups, preferably one hydroxyl group), a C₃-C₇ cycloalkyl group (which may, for example, be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]heptyl or bicyclo[3.1.1]heptyl, preferably cyclopropyl or cyclohexyl, and said C₃-C₇ cycloalkyl group may be substituted with at most 2 hydroxyl group, preferably one hydroxyl group), a C₁-C₇ alkoxy group (which may, for example, be methoxy, ethoxy n-propoxy, i-propoxy, n-

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butoxy, i-butoxy, s-butoxy, t-butoxy, pentyloxy, hexyloxy or heptyloxy, preferably methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy or t-butoxy), a benzyloxy group, a phenyl group, a naphthyl group (which may be an α -naphthyl group, or a β -naphthyl group), a benzyl group, a pyridyl group (which may, for example, be a 2-pyridyl group, a 3-pyridyl group or a 4-pyridyl group, preferably a 2-pyridyl group), a pyrimidinyl group (which may, for example, be a 2-pyrimidinyl group, a 4-pyrimidinyl group or a 5-pyrimidinyl group), a pyridazinyl group (which may, for example, be a 3-pyridazinyl group or a 4-pyridazinyl group), a furanyl group (which may, for example, be a 2-furanyl group or a 3-furanyl group), a thienyl group (which may, for example, be a 2-thienyl group or a 3-thienyl group), a pyrrolyl group (which may, for example, be a 1-pyrrolyl group, a 2-pyrrolyl group or a 3-pyrrolyl group), a pyrazolyl group (which may, for example, be a 1-pyrazolyl group, a 3-pyrazolyl group or a 4-pyrazolyl group), an imidazolyl group (which may, for example, be a 1-imidazolyl group, a 2-imidazolyl group or a 4-imidazolyl group), a pyranyl group (which may, for example, be 2-pyranyl, 3-pyranyl or 4-pyranyl, preferably 2-pyranyl), a quinolyl group (which may, for example, be 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl or 8-quinolyl, preferably 2-quinolyl), a benzoxazolyl group (which may, for example, be a 2-benzoxalyl group, a

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4-benzoxazolyl group, a 5-benzoxazolyl group, a 6-benzoxazolyl group or a 7-benzoxazolyl group, preferably a 2-benzoxazolyl group), a benzothiazolyl group (which may, for example, be a 2-benzothiazolyl group, a 4-benzothiazolyl group, a 5-benzothiazolyl group, a 6-benzothiazolyl group or a 7-benzothiazolyl group, preferably a 2-benzothiazolyl group), or a benzimidazolyl group (which may, for example, be a 1-benzimidazolyl group, a 2-benzimidazolyl group, a 4-benzimidazolyl group or a 5-benzimidazolyl group, preferably a 2-benzimidazolyl group).

When R^2 or R^3 is a phenyl, naphthyl, benzyl, pyridyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyranyl, quinolyl, benzoxazolyl, benzothiazolyl, or benzimidazolyl group, the substituents for such a phenyl, naphthyl, benzyl, pyridyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyranyl, quinolyl, benzoxazolyl, benzothiazolyl, benzimidazolyl group may be as follows.

The C_1 - C_7 alkyl group includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl and n-heptyl. Preferred may, for example, be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl.

The C_1 - C_7 alkoxy group includes, for example, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, pentyloxy, hexyloxy and

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heptyloxy. Preferred may, for example, be methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy or t-butoxy.

The halogen atom may, for example, be a fluorine atom, a chlorine atom, a bromine atom or an iodine atom, preferably, a fluorine atom, a chlorine atom or a bromine atom.

R^4 is a hydrogen atom or a C_1 - C_7 alkyl group (which may, for example, be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl or n-heptyl, preferably methyl), or forms a bond together with R^7 . It is preferably a hydrogen atom or a methyl group, or forms a bond together with R^7 . More preferably, it is a hydrogen atom, or forms a bond together with R^7 .

R^5 is a hydrogen atom or a carboxymethyl group, preferably a hydrogen atom.

R^n is a substituent at the 1-position of an indole ring, and is a hydrogen atom, a C_1 - C_7 alkyl group (such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl and n-heptyl, preferably a C_1 - C_3 alkyl group), a C_3 - C_7 cycloalkyl group (such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, preferably cyclopropyl), a C_1 - C_4 alkoxyethyl group (such as MOM: methoxyethyl, MEM: 2-methoxyethoxyethyl, ethoxyethyl, n-propoxyethyl, i-propoxyethyl, n-butoxyethyl, iBM: isobutyloxyethyl,

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BUM: t-butoxymethyl, POM: pivaloyloxymethyl and SEM: trimethylsilylethoxymethyl, preferably a C₁-C₂ alkoxy methyl group), an aryloxymethyl group (such as BOM: benzyloxymethyl, PMBM: p-methoxybenzyloxymethyl and p-
5 AOM: p-anisyloxymethyl, preferably a benzyloxymethyl group), a C₁-C₄ alkylaminomethyl group (such as dimethylaminomethyl), a substituted acetamidemethyl group (such as Ac_m: acetamidemethyl and Tac_m: trimethylacetamidemethyl), a substituted thiomethyl group
10 (such as MTM: methylthiomethyl, PTM: phenylthiomethyl and Btm: benzylthiomethyl), a carboxyl group, a C₁-C₇ acyl group (such as formyl, acetyl, fluoroacetyl, difluoroacetyl, trifluoroacetyl, chloroacetyl, dichloroacetyl, trichloroacetyl, propionyl, Pv: pivaloyl
15 and tigloyl), an arylcarbonyl group (such as benzoyl, benzoylformyl, benzoylpropionyl and phenylpropionyl), a C₁-C₄ alkoxy carbonyl group (such as methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, i-propoxycarbonyl, n-butoxycarbonyl, i-butoxycarbonyl, BOC: t-butoxycarbonyl,
20 AOC: t-amylloxycarbonyl, VOC: vinyloxycarbonyl, AOC: allyloxycarbonyl, Teoc: 2-(trimethylsilyl)ethoxycarbonyl, and Troc: 2,2,2-trichloroethoxycarbonyl, preferably methoxycarbonyl), an aryloxycarbonyl group (such as Z: benzyloxycarbonyl, p-nitrobenzyloxycarbonyl and MOZ: p-methoxybenzyloxycarbonyl), a C₁-C₄ alkylaminocarbonyl
25 group (such as methylcarbamoyl, Ec: ethylcarbamoyl and n-propylcarbamoyl), an arylaminocarbonyl group (such as

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phenylcarbamoyl), a C₁-C₇ alkoxy group (such as methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, n-pentoxy, n-hexyloxy and n-heptyloxy, preferably a C₁-C₃ alkoxy group), a C₁-C₇ alkoxyalkyloxy group (such as MOMO: methoxymethyloxy, MEMO: methoxyethyloxymethyloxy and BOMO: benzyloxymethyloxy), a trialkylsilyl group (such as TMS: trimethylsilyl, TES: triethylsilyl, TIPS: triisopropylsilyl, DEIPS: diethylisopropylsilyl, DMIPS: dimethylisopropylsilyl, DTBMS: di-t-butylmethylsilyl, IPDMS: isopropyldimethylsilyl, TBDMS: t-butyldimethylsilyl and TDS: t-hexyldimethylsilyl, preferably t-butyldimethylsilyl), a trialkylarylsilyl group (such as DPMS: diphenylmethylsilyl, TBDPS: t-butyldiphenylsilyl, TBMPs: t-butyldimethoxyphenylsilyl and TPS: triphenylsilyl), an alkylsulfonyl group (such as Ms: methane sulfonyl and ethane sulfonyl), and an aryl sulfonyl group (such as benzene sulfonyl, Ts: p-toluene sulfonyl, p-chlorobenzene sulfonyl, MBS: p-methoxybenzene sulfonyl, m-nitrobenzene sulfonyl, iMds: 2,6-dimethoxy-4-methylbenzene sulfonyl, Mds: 2,6-dimethyl-4-methoxybenzene sulfonyl, Mtb: 2,4,6-trimethoxybenzene sulfonyl, Mte: 2,3,5,6-tetramethyl-4-methoxybenzene sulfonyl, Mtr: 2,3,6-trimethyl-4-methoxybenzene sulfonyl, Mts: 2,4,6-trimethylbenzene sulfonyl and Pme: pentamethylbenzene sulfonyl), preferably a hydrogen atom, methyl, ethyl, n-propyl, i-propyl, cyclopropyl, methoxy,

ethoxy, n-propoxy, i-propoxy, methoxymethyl, ethoxymethyl, carboxyl and methoxycarbonyl, preferably a hydrogen atom, methyl, methoxymethyl, carboxyl and methoxycarbonyl.

- 5 Y is bonded on the carbon atom at the 2-, 3-, 4-, 5-, 6- or 7-position of the indole ring, more preferably on the carbon atom at the 2- or 5-position.

In the definition of Y:

- R⁶ is a hydrogen atom, a C₁-C₇ alkyl group (which
10 may, for example, be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl or n-heptyl, preferably methyl) or a C₃-C₇ cycloalkyl group (which may, for example, be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, preferably
15 cyclopropyl). It is preferably a hydrogen atom or methyl, more preferably a hydrogen atom.

- R⁷ is a hydrogen atom, a C₁-C₇ alkyl group (which may, for example, be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl or
20 n-heptyl, preferably methyl) or a C₃-C₇ cycloalkyl group (which may, for example, be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, preferably cyclopropyl), or forms a bond together with R⁴. It is preferably a hydrogen atom, or forms a bond together with
25 R⁴.

X¹ is S or O, preferably S.

X² is S, O or NH, preferably O or S, more preferably

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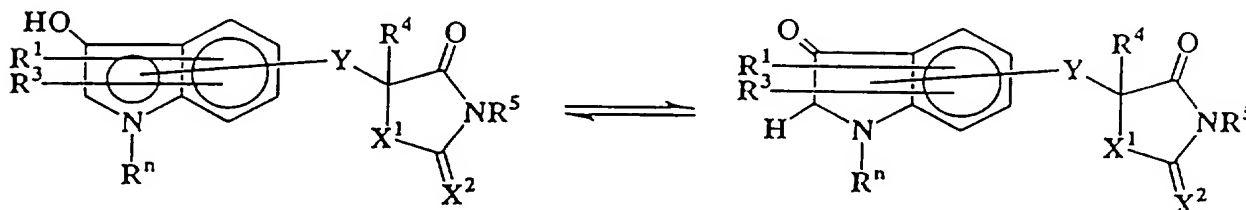
O.

In the present specification, "n" means normal, "i" means iso, "s" means secondary, "t" means tertiary, "c" means cyclo, "Me" means methyl, "Et" means ethyl, "Pr" means propyl, "Bu" means butyl, "Pen" means pentyl, "Hex" means hexyl, "Ph" means phenyl, and "Hal" means halogen.

Among these compounds, there is a compound having an asymmetric carbon atom at the 5-position of thiazolidine ring. The compound having the above formula (I) includes all of these optical isomers and their mixtures.

When R^2 is a substituent at the 3-position of an indole ring and is a hydroxyl group, the following tautomer may form between the 2-position and the 3-position of an indole ring. The present invention includes all of these tautomers.

Indole type thiazolidines of the following formula and their salts.



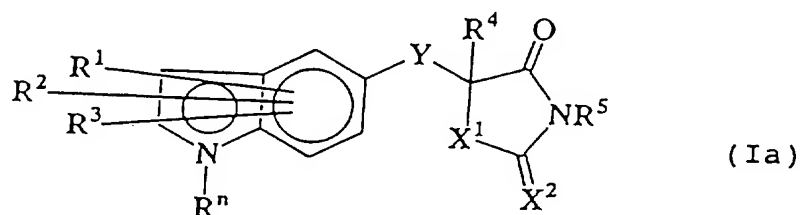
(wherein X^1 , X^2 , Y , R^4 , R^5 and R^n are substituents as defined in the formula (I); R^1 is a substituent at the 2-, 4-, 5-, 6- or 7-position of an indole ring and is a substituent as defined in the formula (I); R^2 is a hydroxyl group at the 3-position of an indole ring; and

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R^3 is a substituent at the 2-, 4-, 5-, 6- or 7-position of an indole ring and is a substituent as defined in the formula (I)).

The following compounds (1) to (24) may be mentioned
5 as preferred examples of the compound of the formula (I) of the present invention.

(1) The indole type thiazolidine compound and its salt of the present invention, wherein the compound of the formula (I) is represented by the following formula
10 (Ia):



15 wherein R^1 is a substituent at the 2-, 3-, 4-, 6- or 7-position of an indole ring, and is a hydrogen atom, a C_1 - C_{10} alkyl group, a C_2 - C_{10} alkenyl group, a C_2 - C_{10} alkynyl group, a C_1 - C_{10} alkoxy group, a C_2 - C_{10} alkenyloxy group, a C_1 - C_{10} alkylthio group, a C_1 - C_{10} monoalkylamino group or a
20 di- C_1 - C_{10} alkylamino group (each of said C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_1 - C_{10} alkoxy, C_2 - C_{10} alkenyloxy, C_1 - C_{10} alkylthio, C_1 - C_{10} monoalkylamino and di- C_1 - C_{10} alkylamino groups may be substituted with a hydroxyl group or a C_1 - C_7 alkyl group), or

25 $-W_k-W_l-Z$ (among groups of Z as defined for the formula (I), said C_3 - C_{10} cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl,

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cyclooctyl, cyclononyl, cyclodecyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, or adamantyl, said C₃-C₇ cycloalkenyl group is cyclohexenyl, cyclopentadienyl, 2-bicyclo[2.2.1]heptenyl or 2,5-bicyclo[2.2.1]heptadienyl, said C₆-C₁₄ aromatic group is phenyl, naphthyl, indenyl, indanyl or fluorenyl, said C₁-C₁₂ heterocyclic aromatic group is furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, furazanyl, pyrazolyl, oxopyrazolyl, imidazolyl, 10 oxoimidazolyl, triazolyl, triazolonyl, tetrazolyl, pyranyl, pyridyl, pyridonyl, pyridazinyl, pyridazinonyl, pyrimidinyl, pyrimidinonyl, pyrazinyl, triazinyl, tetrazinyl, indolyl, quinolyl, quinolonyl, benzofuranyl, benzothienyl, isoquinolyl, isoquinolonyl, benzoxazolyl, 15 benzothiazolyl, benzopyrazolyl, benzimidazolyl, benzotriazolyl, benzopyranyl, indoliziny, purinyl, phthalazinyl, oxophthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzodioxolyl, benzodioxanyl, oxonaphthalenyl, dihydrobenzofuranyl, 20 benzothiazinyl, pteridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[5,1-c][1,2,4]triazinyl, thiazolo[3,2-b]triazolyl, benzopyrano[2,3-b]pyridyl, 5H-benzopyrano[2,3-b]pyridonyl, xanthenyl, phenoxathiinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, 25 phenoxazinyl, or thianthrenyl, and said C₁-C₆ heterocycloaliphatic group is piperidyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, morpholinyl, or

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tetrahydrofuranyl, (each of said C₃-C₁₀ cycloalkyl, C₃-C₇ cycloalkenyl, C₆-C₁₄ aromatic, C₁-C₁₂ heterocyclic aromatic and C₁-C₆ heterocycloaliphatic groups may have at most 5 substituents selected from the group consisting

5 of a hydrogen atom, a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group, a C₃-C₇ cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C₁-C₇ alkoxy group, a C₁-C₇ alkylthio group, a halogen atom, a

10 trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C₁-C₃ alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy

15 group, a tri-C₁-C₇-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group

20 consisting of a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group, a C₁-C₃ alkoxy group, a C₁-C₃ alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a

25 thiazolidindion-5-yl group and a thiazolidindion-5-yl methyl group),

V is O, S, SO, SO₂ or NR⁸ (R⁸ is a hydrogen atom or a

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C₁-C₃ alkyl group),

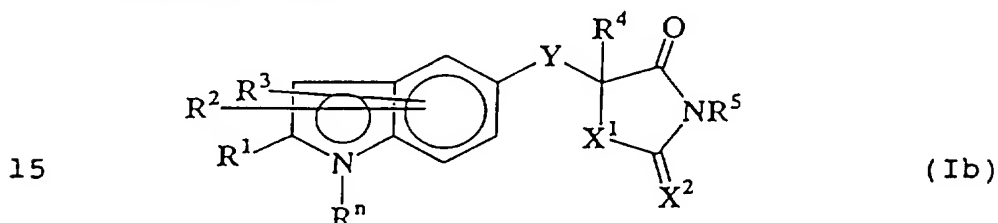
W is a divalent C₁-C₆ saturated or C₂-C₆ unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C₁-C₇ alkyl groups, and

5 each of k and ℓ is 0 or 1),

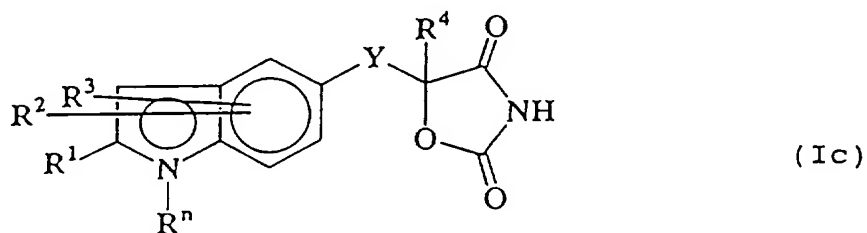
-V-W-Z (V, W and Z are as defined above), or

-W-V-W-Z (V, W and Z are as defined above, and two W's may be the same or different).

(2) The indole type thiazolidine compound and its
10 salt according to the above-mentioned (1), wherein the compound of the formula (Ia) is represented by the formula (Ib):



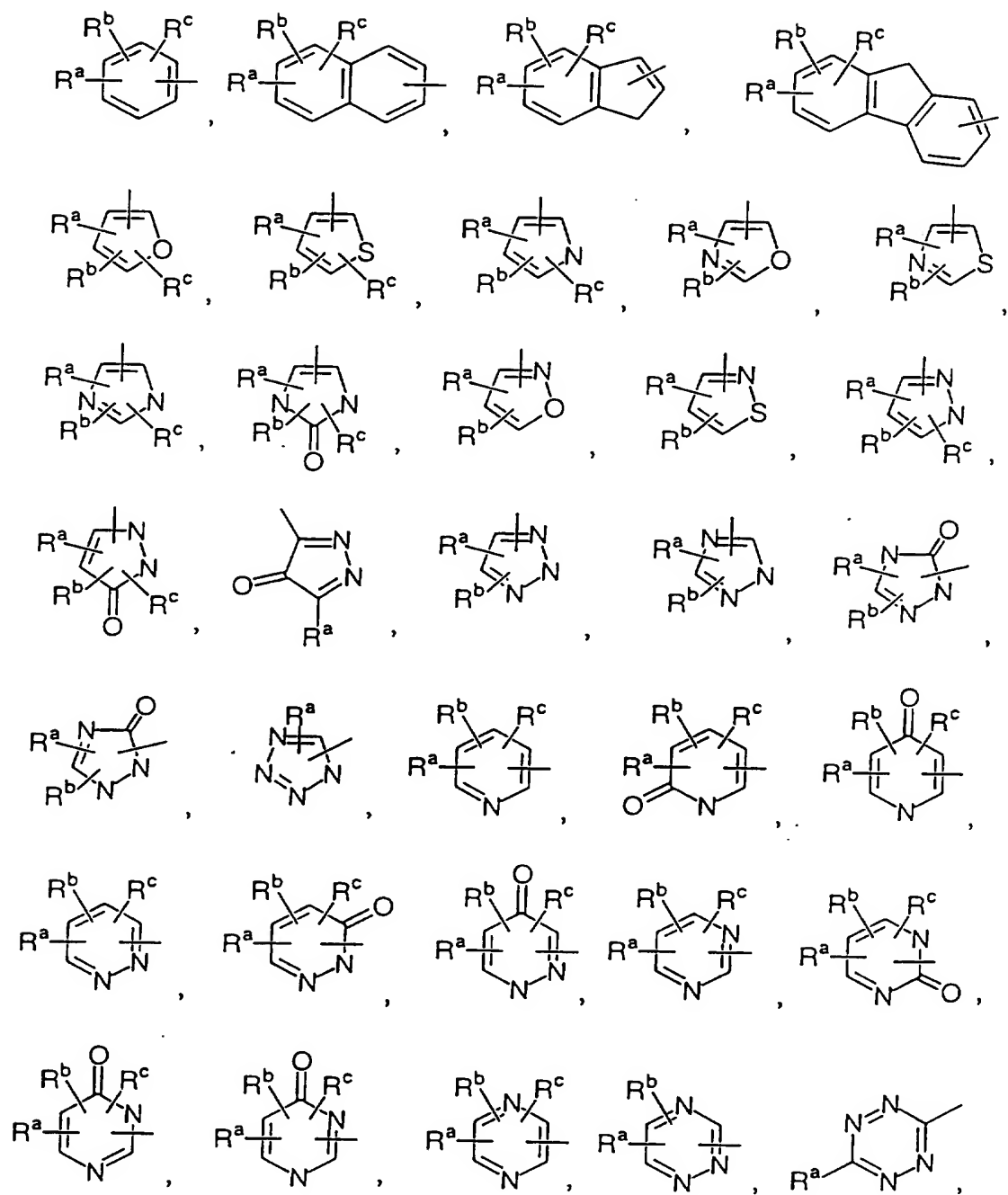
(3) The indole type thiazolidine compound and its
salt according to the above-mentioned (2), wherein the
compound of the formula (Ib) is represented by the
20 following formula (Ic):

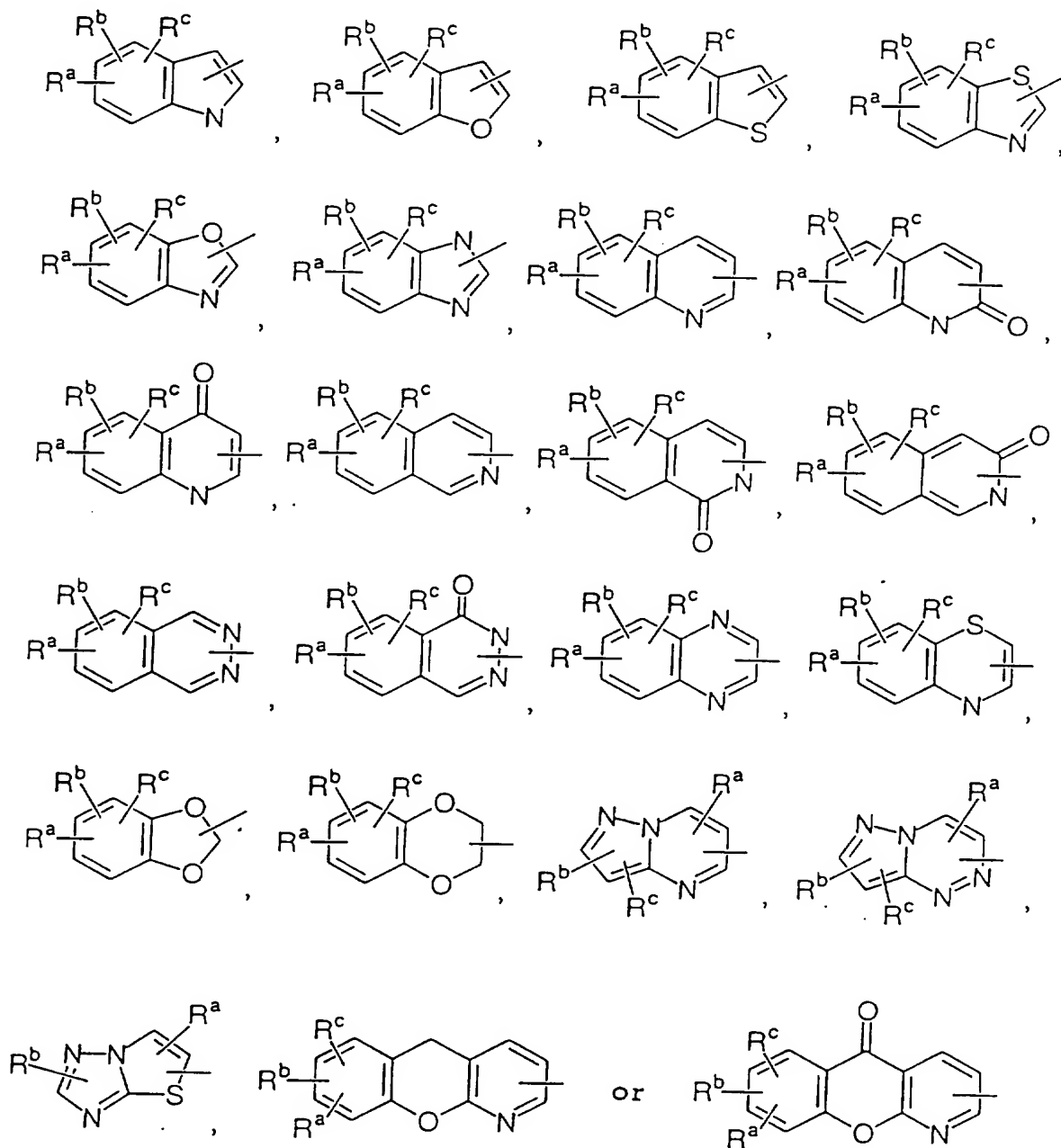


25 wherein R¹ is a substituent at the 2-position of an indole ring, and is -W-Z, -V-Z, -W-V-Z, -V-W-Z or -W-V-W-Z (V is O, S, SO, SO₂ or NR⁸ (R⁸ is a hydrogen

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atom or a C₁-C₃ alkyl group), W is a divalent C₁-C₆ saturated or C₂-C₆ unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C₁-C₇ alkyl groups, when two W's are present, such W's
5 may be the same or different, and Z is





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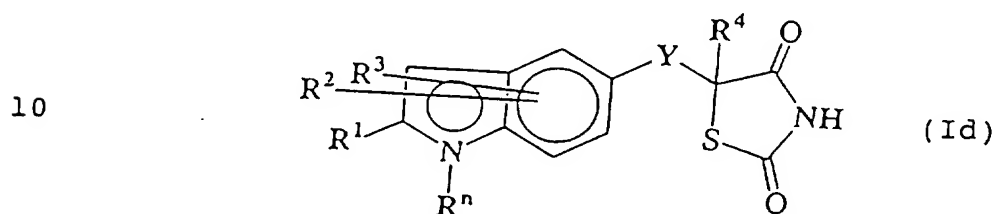
wherein each of R^a and R^b is independently a hydrogen atom, a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group, a C_3 - C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1 - C_7 alkoxy group, a C_1 - C_7 alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1 - C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri- C_1 - C_7 -alkylsilyloxy group, a phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group, a C_1 - C_3 alkoxy group, a C_1 - C_3 alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group or a hydroxymethyl group);

R^2 or R^3 is a hydrogen atom, a C_1 - C_4 alkyl group, a

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C_3 - C_6 cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and R^5 is a hydrogen atom.

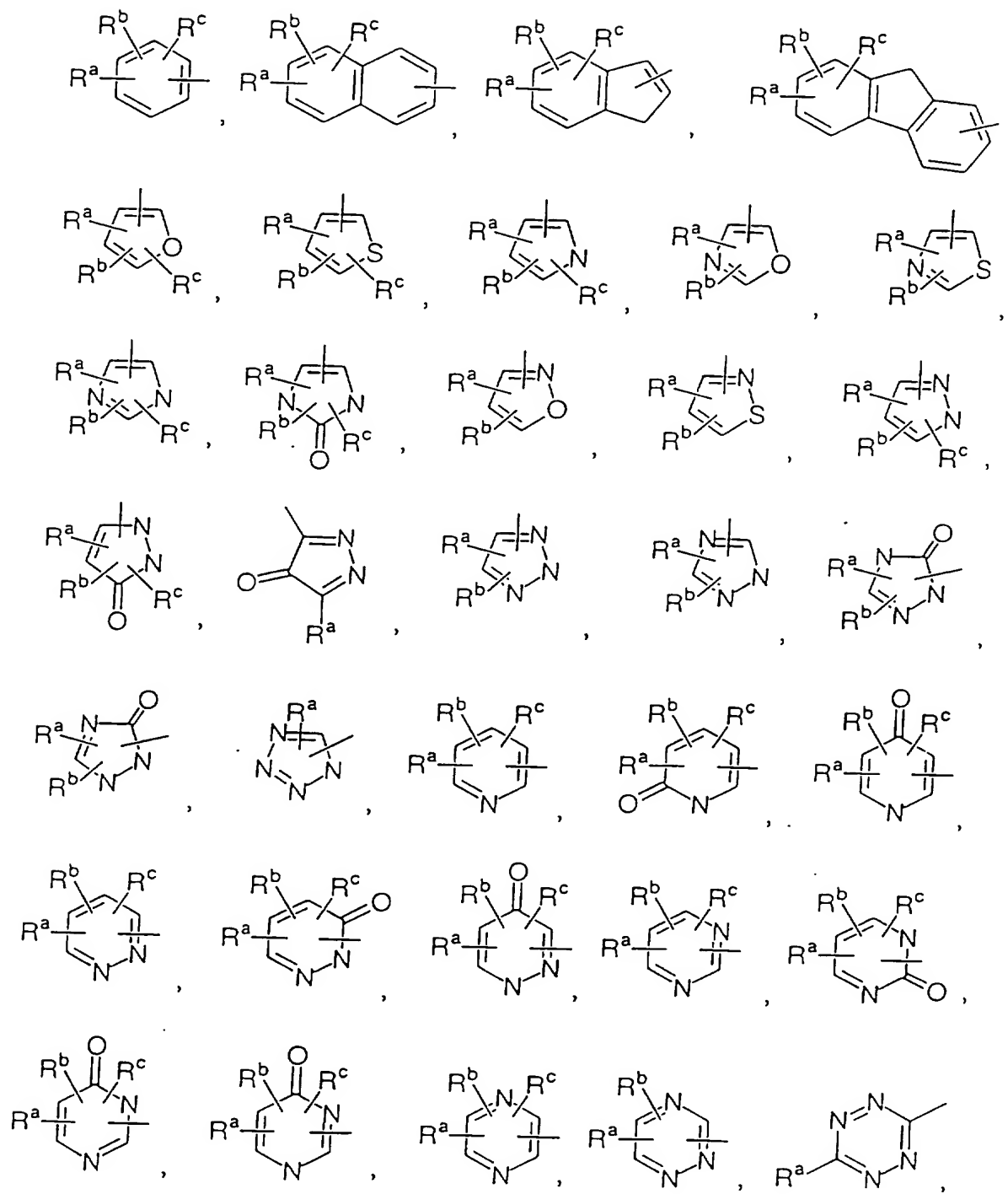
(4) The indole type thiazolidine compound and its salt according to the above-mentioned (2), wherein the compound of the formula (Ib) is represented by the following formula (Id):

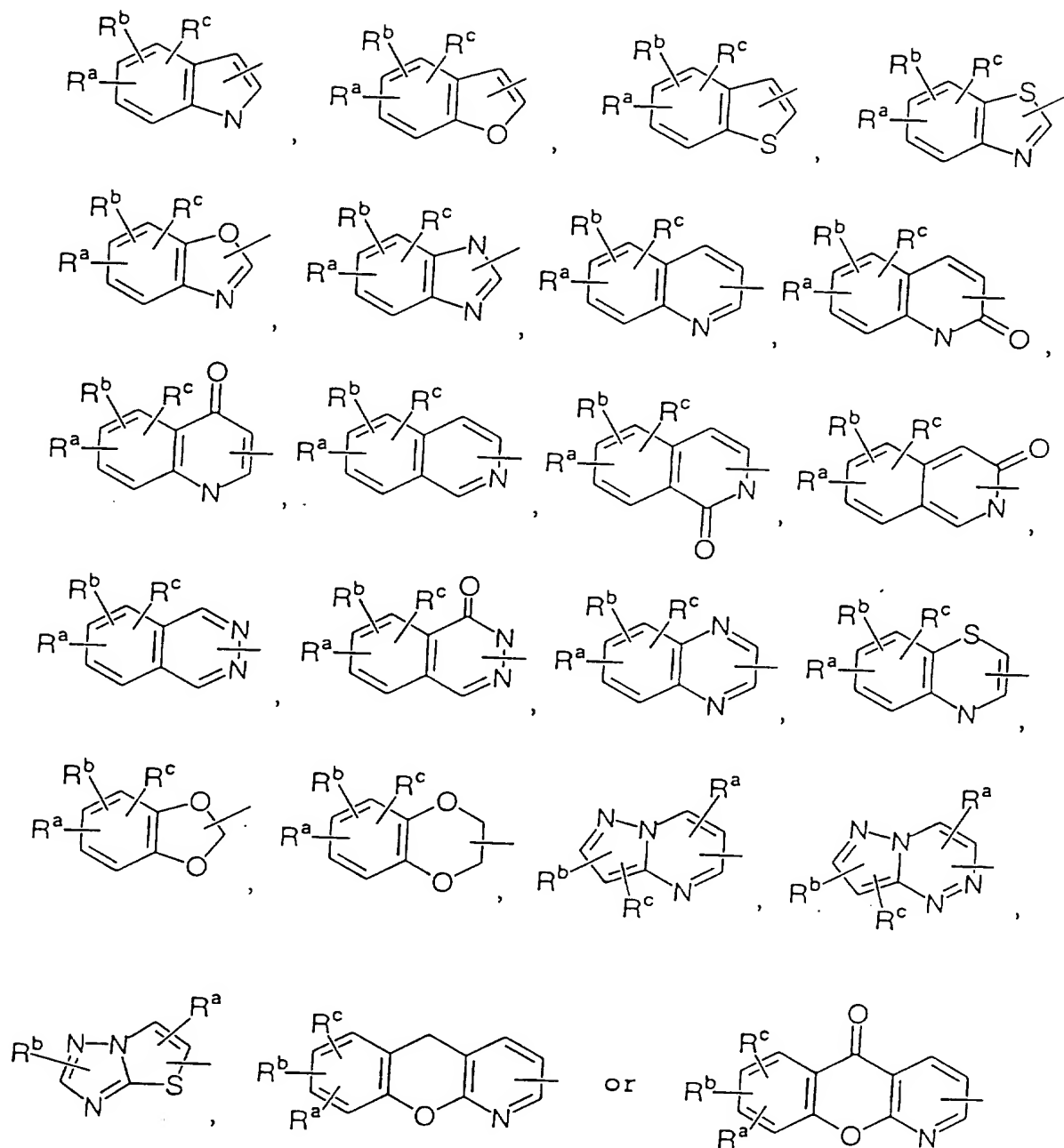


wherein R^1 is a substituent at the 2-position of an indole ring, and is $-W-Z$, $-V-Z$, $-W-V-Z$, $-V-W-Z$ or $-W-V-W-Z$ (V is O , S , SO , SO_2 or NR^8 (R^8 is a hydrogen atom or a C_1 - C_3 alkyl group)), W is a divalent C_1 - C_6 saturated or C_2 - C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1 - C_7 alkyl groups, when two W 's are present, such W 's may be the same or different, and Z is

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wherein each of R^a and R^b is independently a hydrogen atom, a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group, a C_3 - C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1 - C_7 alkoxy group, a C_1 - C_7 alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1 - C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri- C_1 - C_7 -alkylsilyloxy group, a phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group, a C_1 - C_3 alkoxy group, a C_1 - C_3 alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group or a hydroxymethyl group);

R^2 or R^3 is a hydrogen atom, a C_1 - C_4 alkyl group, a

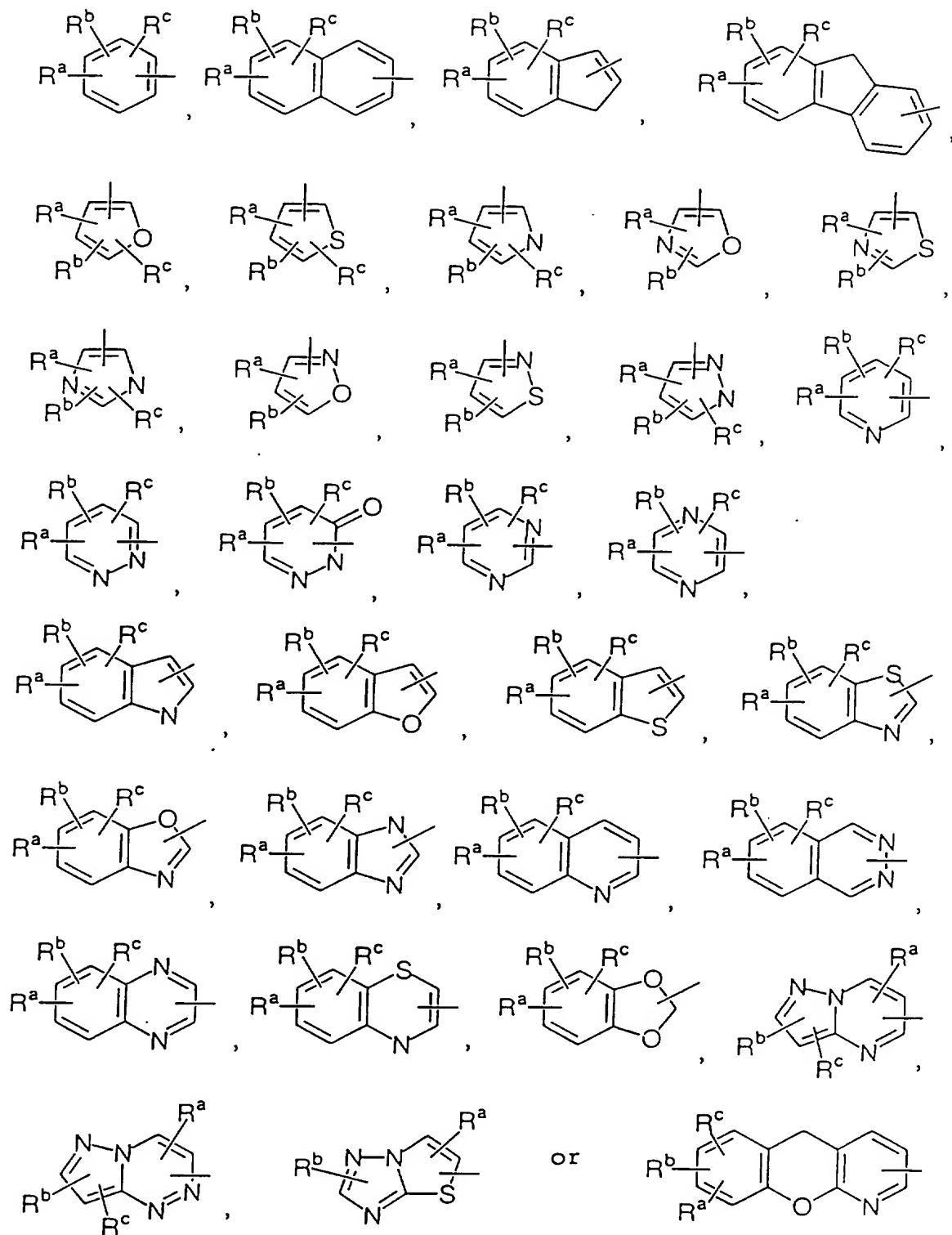
- 53 -

C₃-C₆ cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and

R⁵ is a hydrogen atom.

(5) The indole type thiazolidine compound and its
5 salt according to the above-mentioned (4), wherein: Y is CR⁶R⁷ (R⁶ is a hydrogen atom or a methyl group, and R⁷ is a hydrogen atom, or forms a bond together with R⁴);

R¹ is a substituent at the 2-position of an indole ring, and is -W-Z, -V-Z, -W-V-Z, -V-W-Z or -W-V-W-Z (V is
10 O, S, SO, SO₂ or NR⁸ (R⁸ is a hydrogen atom or a C₁-C₃ alkyl group), W is a divalent C₁-C₆ saturated or C₂-C₆ unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C₁-C₇ alkyl groups (provided that the first carbon atom bonded to N is not
15 substituted with a hydroxyl group, and also provided that the first carbon atom bonded to O is not substituted with a hydroxyl group or an oxo group) when two W's are present, such W's may be the same or different, and Z is



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wherein each R^a and R^b is independently a hydrogen atom, a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group, a C_3 - C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1 - C_7 alkoxy group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1 - C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a phenoxy group, a benzyloxy group, a tri- C_1 - C_7 -alkylsilyloxy group, a phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group, a C_1 - C_3 alkoxy group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group or a hydroxymethyl group);

R^4 is a hydrogen atom or a methyl group, or forms a bond together with R^7 ; and

R^n is a substituent at the 1-position of an indole

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ring, and is a hydrogen atom, a C₁-C₃ alkyl group, a cyclopropyl group, a C₁-C₂ alkoxymethyl group, a benzyloxymethyl group, a carboxyl group, a methoxycarbonyl group, a C₁-C₃ alkoxy group, and a
 5 trialkylsilyl group.

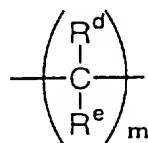
(6) The indole type thiazolidine compound and its salt according to the above-mentioned (5), wherein:

R¹ is -W-Z, wherein W is a divalent C₁-C₆ saturated or C₂-C₆ unsaturated hydrocarbon group which may be
 10 substituted with at most 2 of hydroxyl, oxo and C₁-C₇ alkyl groups.

(7) The indole type thiazolidine compound and its salt according to the above-mentioned (6), wherein:

R¹ is -W-Z, wherein W is

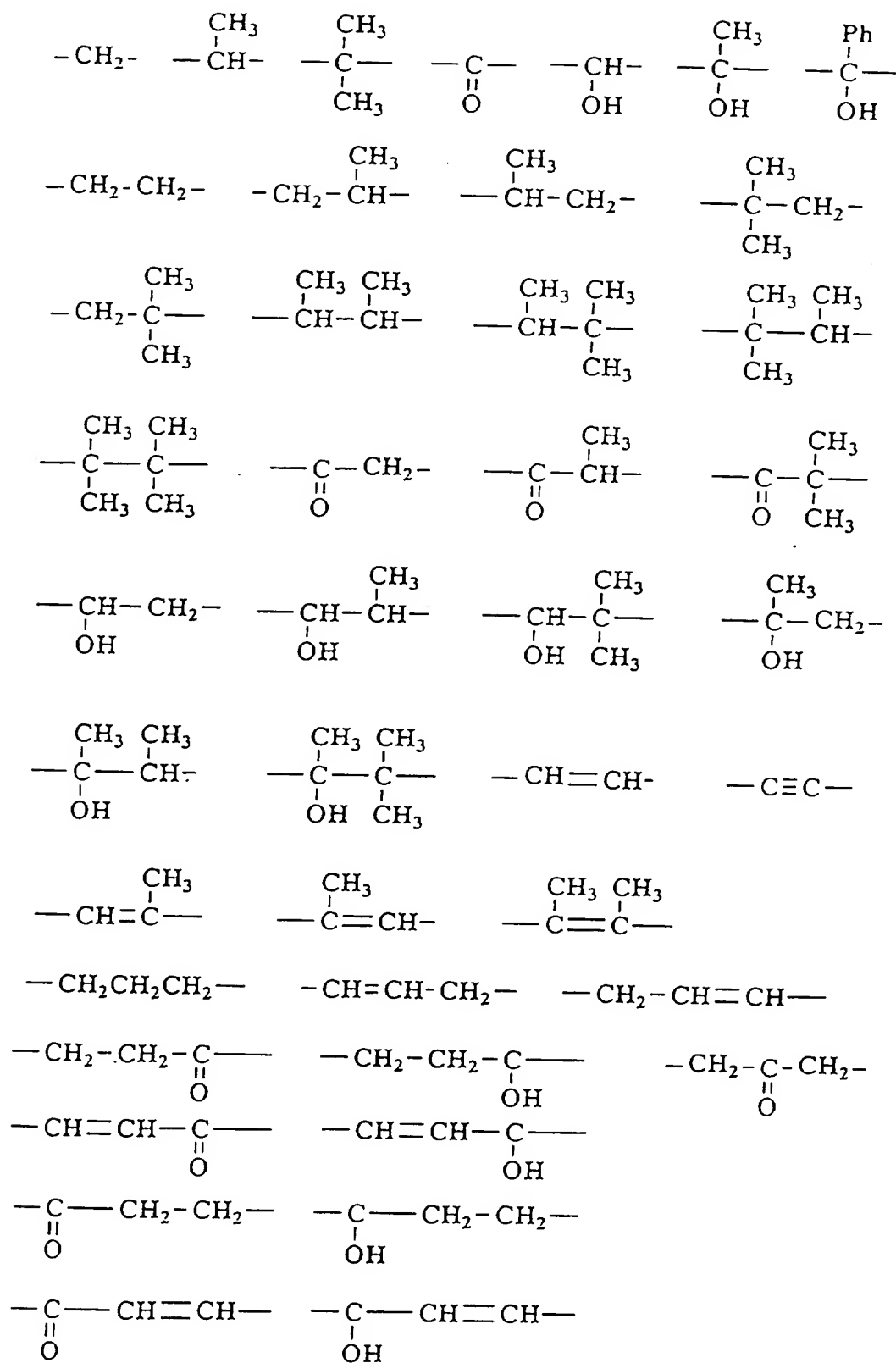
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wherein m is from 1 to 5, and each of R^d and R^e is independently a hydrogen atom, a methyl group or a
 20 hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d's together form a double bond, or adjacent R^d's and R^e's together form a triple bond.

(8) The indole type thiazolidine compound and its salt according to the above-mentioned (7), wherein:

25 R¹ is -W-Z, wherein W is



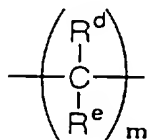
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(9) The indole type thiazolidine compound and its salt according to the above-mentioned (5), wherein:

R^1 is -V-Z, wherein V is S, SO or SO₂.

(10) The indole type thiazolidine compound and its salt according to the above-mentioned (5), wherein:

R^1 is -W-V-Z, wherein W is



wherein m is from 1 to 5, and each of R^d and R^e is independently a hydrogen atom, a methyl group or a hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d 's together form a double bond, or adjacent R^d 's and R^e 's together form a triple bond (provided that R^d and R^e on the first carbon atom adjacent to N are not hydroxyl groups and also provided that R^d and R^e on the first carbon atom adjacent to O are not hydroxyl groups or do not together form an oxo group),

V is NR⁸ (R⁸ is a hydrogen atom or a C₁-C₃ alkyl group).

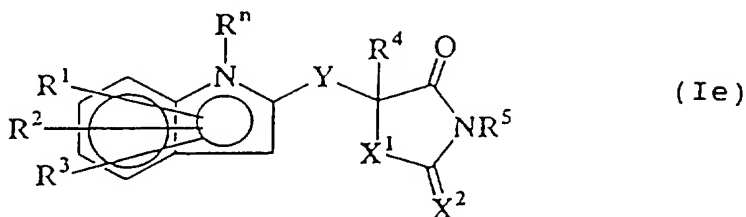
(11) The indole type thiazolidine compound and its salt according to the above-mentioned (10), wherein:

R^1 is -W-V-Z, wherein -W-V- is -CO-NR⁸- (R⁸ is a hydrogen atom or a C₁-C₃ alkyl group).

(12) The indole type thiazolidine compound and its salt of the present invention, wherein the compound of the formula (I) is represented by the following formula

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(Ie):



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 wherein R^1 is a substituent at the 3-, 4-, 5-, 6- or 7-
 position of an indole ring, and is a C_1 - C_{10} alkyl group,
 a C_2 - C_{10} alkenyl group, a C_2 - C_{10} alkynyl group, a C_1 - C_{10}
 alkoxy group, a C_2 - C_{10} alkenyloxy group, a C_1 - C_{10}
 10 alkylthio group, a C_1 - C_{10} monoalkylamino group or a di-
 C_1 - C_{10} alkylamino group (each of said C_1 - C_{10} alkyl, C_2 - C_{10}
 alkenyl, C_2 - C_{10} alkynyl, C_1 - C_{10} alkoxy, C_2 - C_{10} alkenyloxy,
 C_1 - C_{10} alkylthio, C_1 - C_{10} monoalkylamino and di- C_1 - C_{10}
 alkylamino groups may be substituted with a hydroxyl
 15 group or a C_1 - C_7 alkyl group), or

- W_k - V_t -Z (among groups of Z as defined for the
 formula (I), said C_3 - C_{10} cycloalkyl group is cyclopropyl,
 cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl,
 cyclooctyl, cyclononyl, cyclodecyl, bicyclo[2.2.1]heptyl,
 20 bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, or adamantyl,
 said C_3 - C_7 cycloalkenyl group is cyclohexenyl,
 cyclopentadienyl, 2-bicyclo[2.2.1]heptenyl or 2,5-
 bicyclo[2.2.1]heptadienyl, said C_6 - C_{14} aromatic group is
 phenyl, naphthyl, indenyl, indanyl or fluorenyl, said C_1 -
 25 C_{12} heterocyclic aromatic group is furyl, thienyl,
 pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl,
 furazanyl, pyrazolyl, oxopyrazolyl, imidazolyl,

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oxoimidazolyl, triazolyl, triazolonyl, tetrazolyl, pyranyl, pyridyl, pyridonyl, pyridazinyl, pyridazinonyl, pyrimidinyl, pyrimidinonyl, pyrazinyl, triazinyl, tetrazinyl, indolyl, quinolyl, quinolonyl, benzofuranyl, benzothienyl, isoquinolyl, isoquinolonyl, benzoxazolyl, benzothiazolyl, benzopyrazolyl, benzimidazolyl, benzotriazolyl, benzopyranyl, indoliziny, purinyl, phthalazinyl, oxophthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzodioxolyl, benzodioxanyl, oxonaphthalenyl, dihydrobenzofuranyl, benzothiazinyl, pteridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[5,1-c][1,2,4]triazinyl, thiazolo[3,2-b]triazolyl, benzopyrano[2,3-b]pyridyl, 5H-benzopyrano[2,3-b]pyridonyl, xanthenyl, phenoxathiinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, or thianthrenyl, and said C₁-C₆ heterocycloaliphatic group is piperidyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, morpholinyl, or tetrahydrofuranyl, (each of said C₃-C₁₀ cycloalkyl, C₃-C₇ cycloalkenyl, C₆-C₁₄ aromatic, C₁-C₁₂ heterocyclic aromatic and C₁-C₆ heterocycloaliphatic groups may have at most 5 substituents selected from the group consisting of a hydrogen atom, a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group, a C₃-C₇ cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C₁-C₇ alkoxy group, a C₁-C₇ alkylthio group, a halogen atom, a

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trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C₁-C₃ alkoxy carbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C₁-C₇-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group, a C₁-C₃ alkoxy group, a C₁-C₃ alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group and a thiazolidindion-5-yl methyl group),

V is O, S, SO, SO₂ or NR⁸ (R⁸ is a hydrogen atom or a C₁-C₃ alkyl group),

W is a divalent C₁-C₆ saturated or C₂-C₆ unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C₁-C₇ alkyl groups, and each of k and ℓ is 0 or 1),

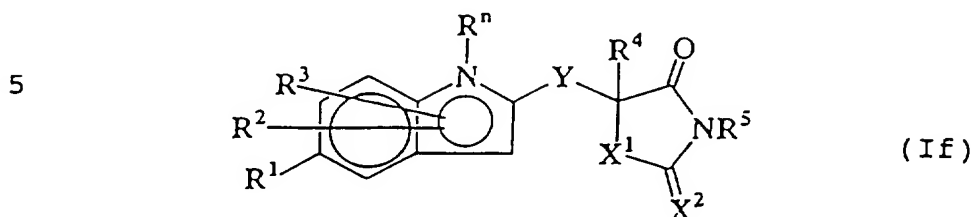
-V-W-Z (V, W and Z are as defined above), or

-W-V-W-Z (V, W and Z are as defined above, and two W's may be the same or different).

(13) The indole type thiazolidine compound and its

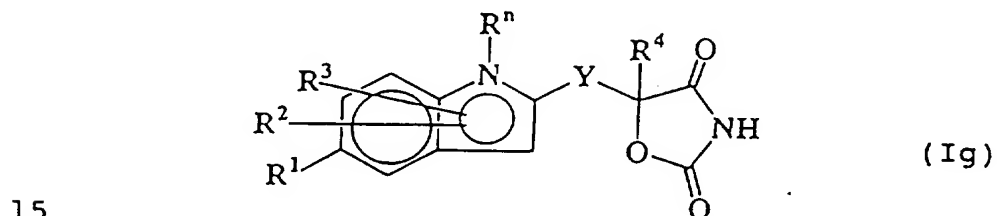
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salt according to the above-mentioned (12), wherein the compound of the formula (Ie) is represented by the formula (If):



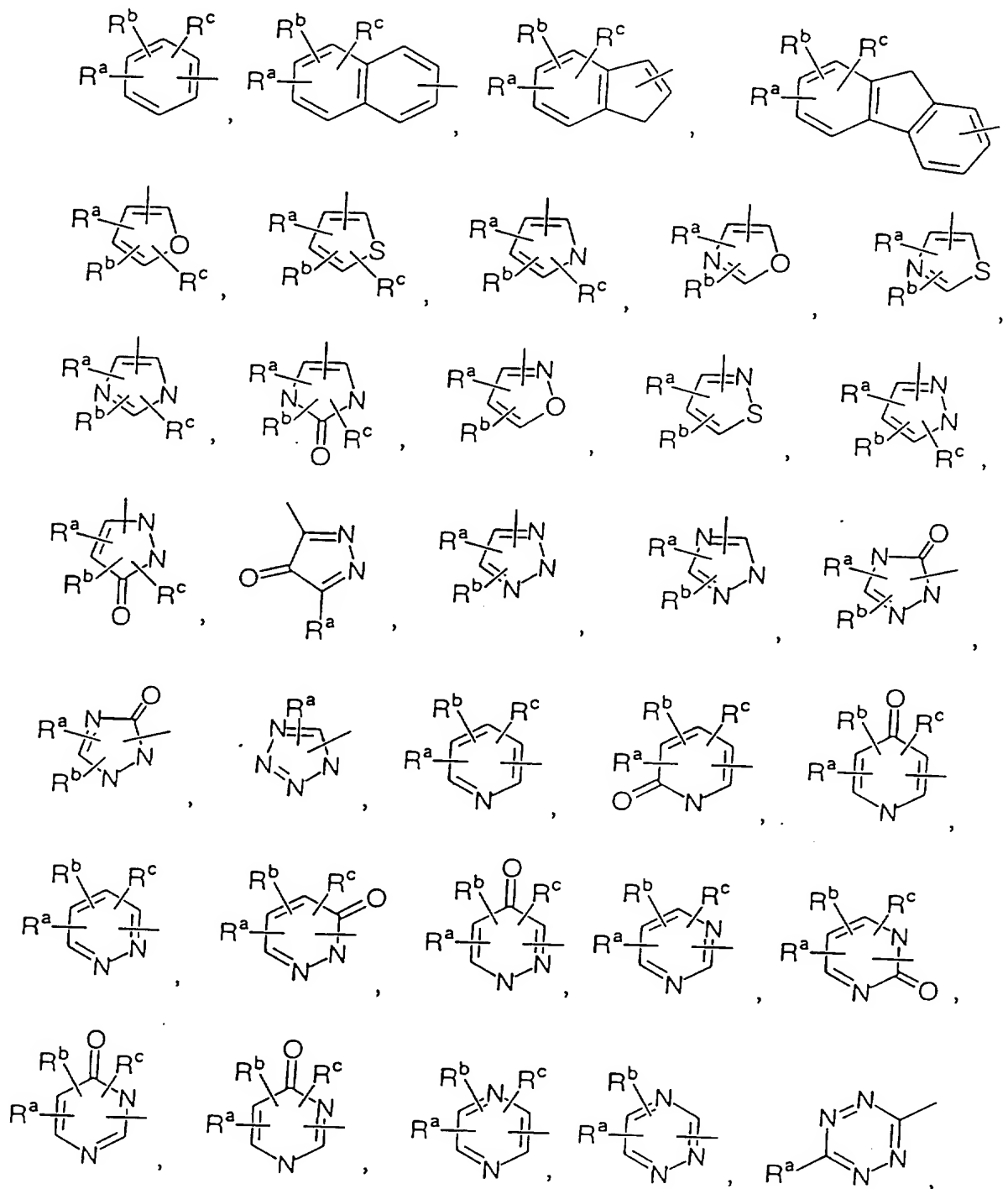
(14) The indole type thiazolidine compound and its salt according to the above-mentioned (13), wherein the compound of the formula (If) is represented by the following formula (Ig):

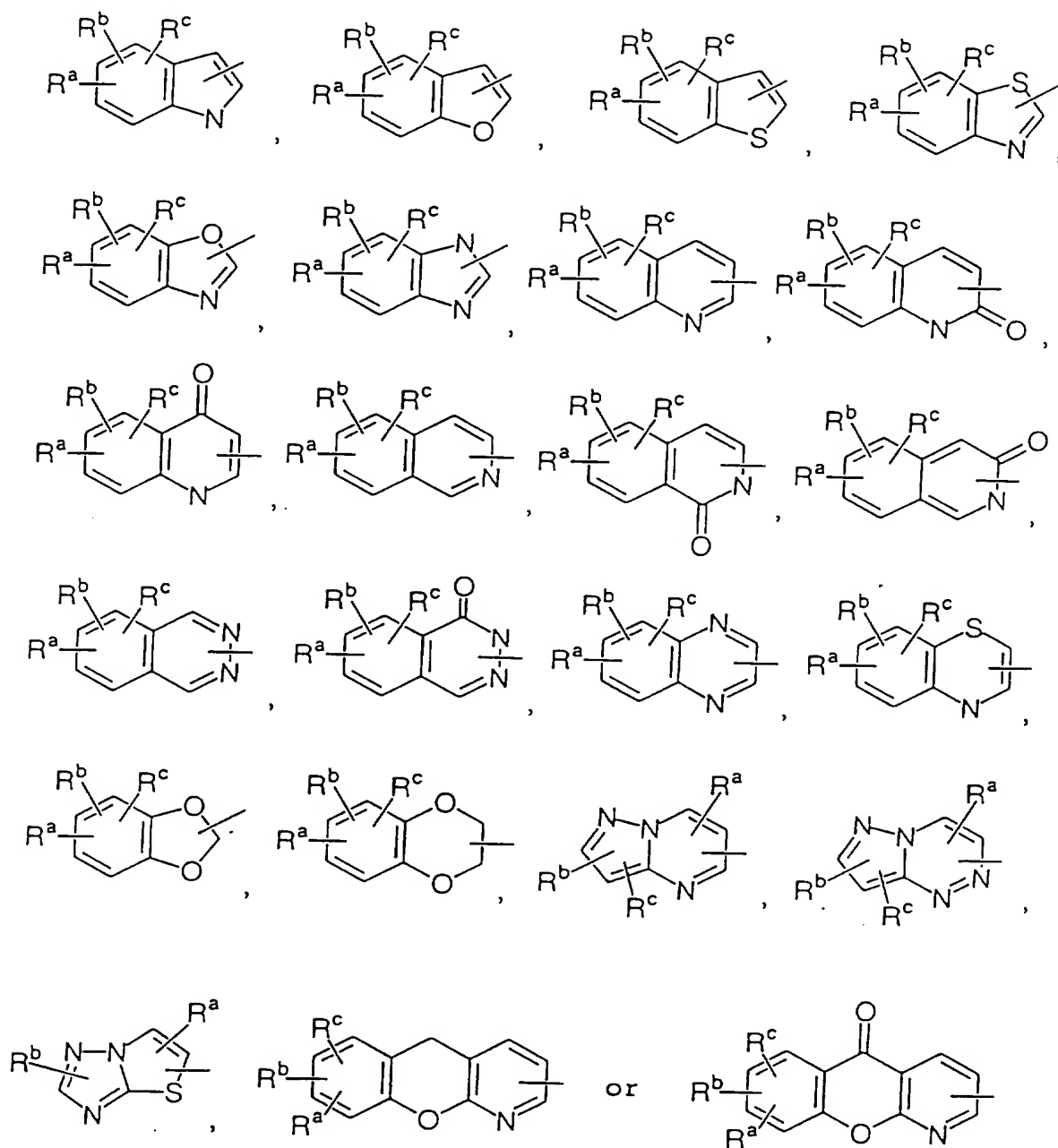
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wherein R^1 is a substituent at the 5-position of an indole ring, and is $-W-Z$, $-V-Z$, $-W-V-Z$, $-V-W-Z$ or $-W-V-W-Z$ (V is O , S , SO , SO_2 or NR^8 (R^8 is a hydrogen atom or a C_1 - C_3 alkyl group), W is a divalent C_1 - C_6 saturated or C_2 - C_6 unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C_1 - C_7 alkyl groups, when two W 's are present, such W 's may be the same or different, and Z is

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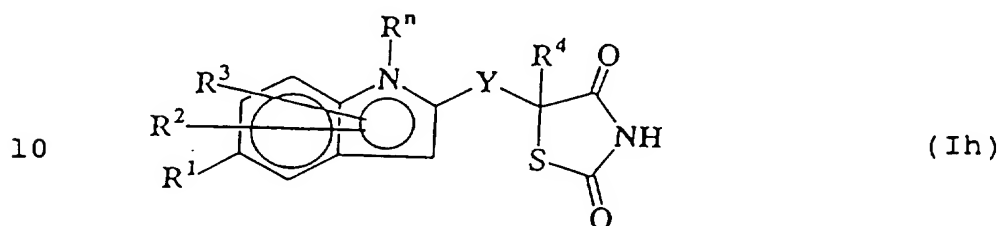
wherein each of R^a and R^b is independently a hydrogen atom, a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group, a C_3 - C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1 - C_7 alkoxy group, a C_1 - C_7 alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1 - C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri- C_1 - C_7 -alkylsilyloxy group, a phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group, a C_1 - C_3 alkoxy group, a C_1 - C_3 alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group or a hydroxymethyl group);

R^2 or R^3 is a hydrogen atom, a C_1 - C_4 alkyl group, a

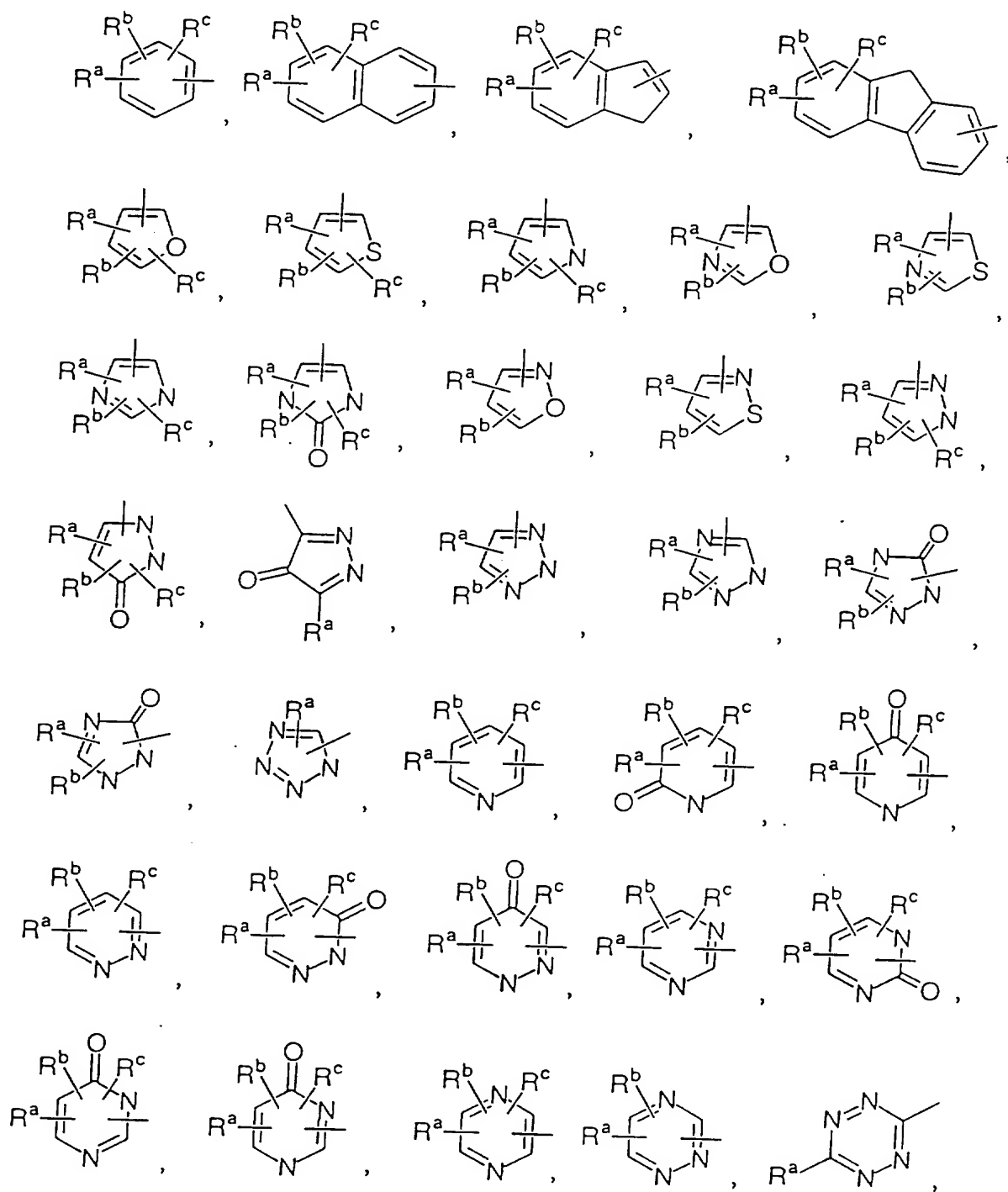
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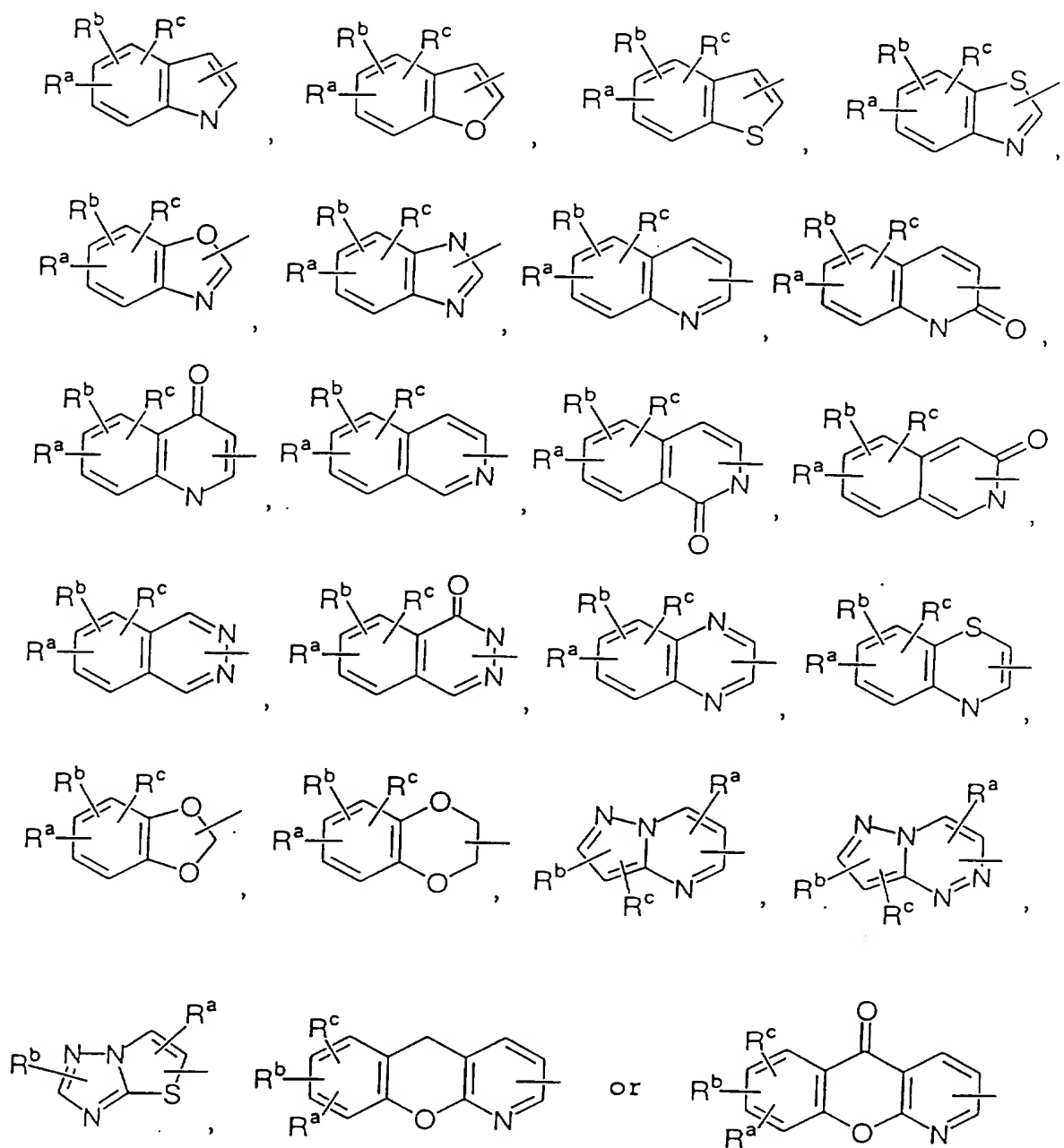
C₃-C₆ cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and R⁵ is a hydrogen atom.

(15) The indole type thiazolidine compound and its salt according to the above-mentioned (13), wherein the compound of the formula (If) is represented by the following formula (Ih):



wherein R¹ is -V-W-Z, -W-Z, -V-W-V-W-Z, -W-V-W-Z, -V-W-V-Z or -W-V-Z (V is O, S or NR⁸ (R⁸ is a hydrogen atom or a C₁-C₃ alkyl group), W is a divalent C₁-C₆ saturated or C₂-C₆ unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C₁-C₇ alkyl groups, when two V's or W's are present, such V's or W's may be the same or different, and Z is





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wherein each of R^a and R^b is independently a hydrogen atom, a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group, a C_3 - C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1 - C_7 alkoxy group, a C_1 - C_7 alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1 - C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri- C_1 - C_7 -alkylsilyloxy group, a phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group, a C_1 - C_3 alkoxy group, a C_1 - C_3 alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group or a hydroxymethyl group);

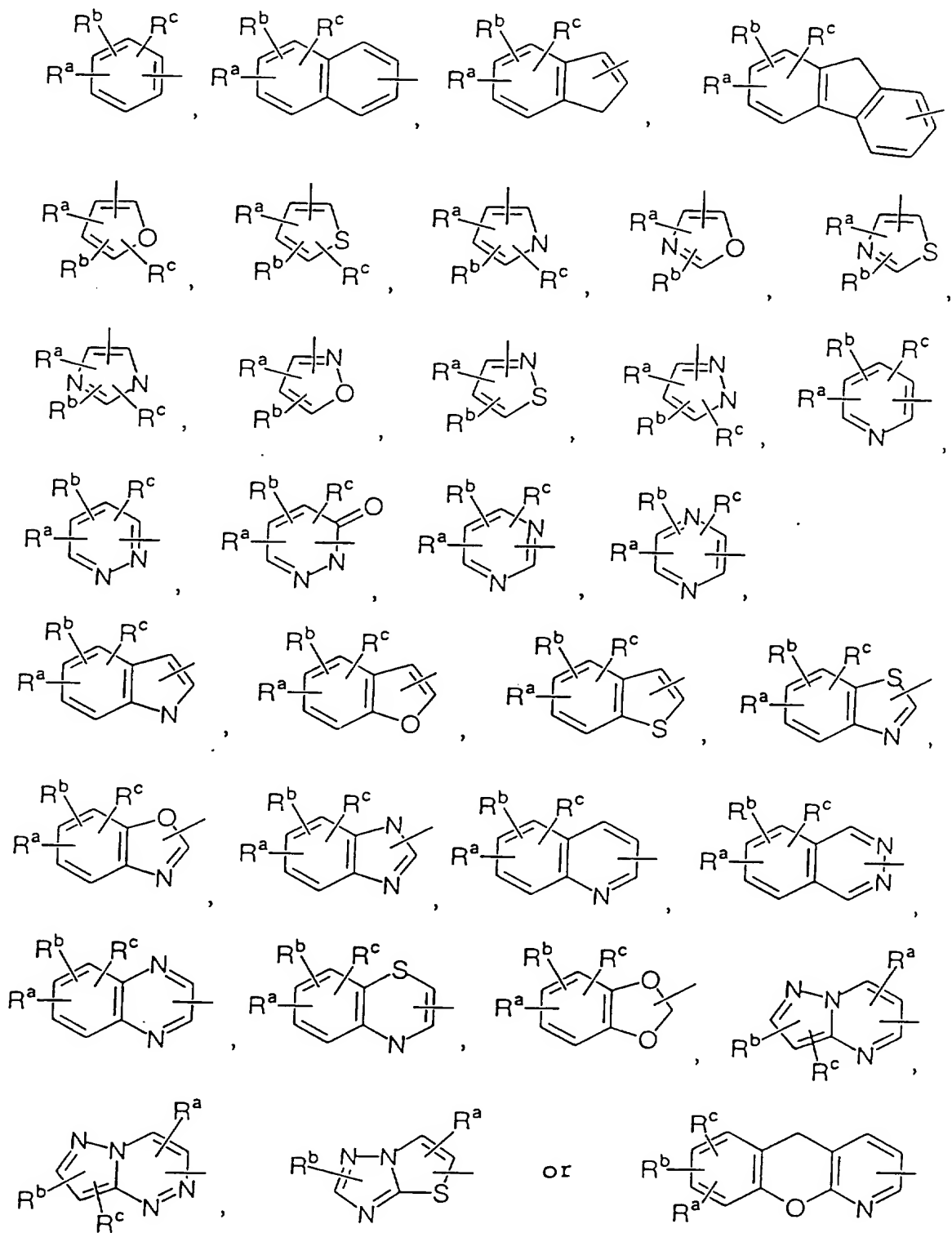
R^2 or R^3 is a hydrogen atom, a C_1 - C_4 alkyl group, a

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C₃-C₆ cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and R⁵ is a hydrogen atom.

(16) The indole type thiazolidine compound and its salt according to the above-mentioned (15), wherein: Y is CR⁶R⁷ (R⁶ is a hydrogen atom or a methyl group, and R⁷ is a hydrogen atom, or forms a bond together with R⁴);

R¹ is a substituent at the 5-position of an indole ring, and is -W-Z, -V-Z, -W-V-Z, -V-W-Z or -W-V-W-Z (V is O, S, SO, SO₂ or NR⁸ (R⁸ is a hydrogen atom or a C₁-C₃ alkyl group), W is a divalent C₁-C₆ saturated or C₂-C₆ unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C₁-C₇ alkyl groups (provided that the first carbon atom bonded to N is not substituted with a hydroxyl group, and also provided that the first carbon atom bonded to O is not substituted with a hydroxyl group or an oxo group), when two W's are present, such W's may be the same or different, and Z is



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wherein each R^a and R^b is independently a hydrogen atom, a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group, a C_3 - C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1 - C_7 alkoxy group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1 - C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a phenoxy group, a benzyloxy group, a tri- C_1 - C_7 -alkylsilyloxy group, a phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group, a C_1 - C_3 alkoxy group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group or a hydroxymethyl group);

R^4 is a hydrogen atom or a methyl group, or forms a bond together with R^7 ; and

R^n is a substituent at the 1-position of an indole

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ring, and is a hydrogen atom, a C₁-C₃ alkyl group, a cyclopropyl group, a C₁-C₂ alkoxymethyl group, a benzyloxymethyl group, a carboxyl group, a methoxycarbonyl group, a C₁-C₃ alkoxy group, and a
 5 trialkylsilyl group.

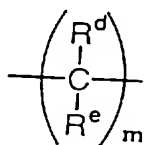
(17) The indole type thiazolidine compound and its salt according to the above-mentioned (16), wherein:

R¹ is -W-Z, wherein W is a divalent C₁-C₆ saturated or C₂-C₆ unsaturated hydrocarbon group which may be
 10 substituted with at most 2 of hydroxyl, oxo and C₁-C₇ alkyl groups.

(18) The indole type thiazolidine compound and its salt according to the above-mentioned (17), wherein:

R¹ is -W-Z, wherein W is

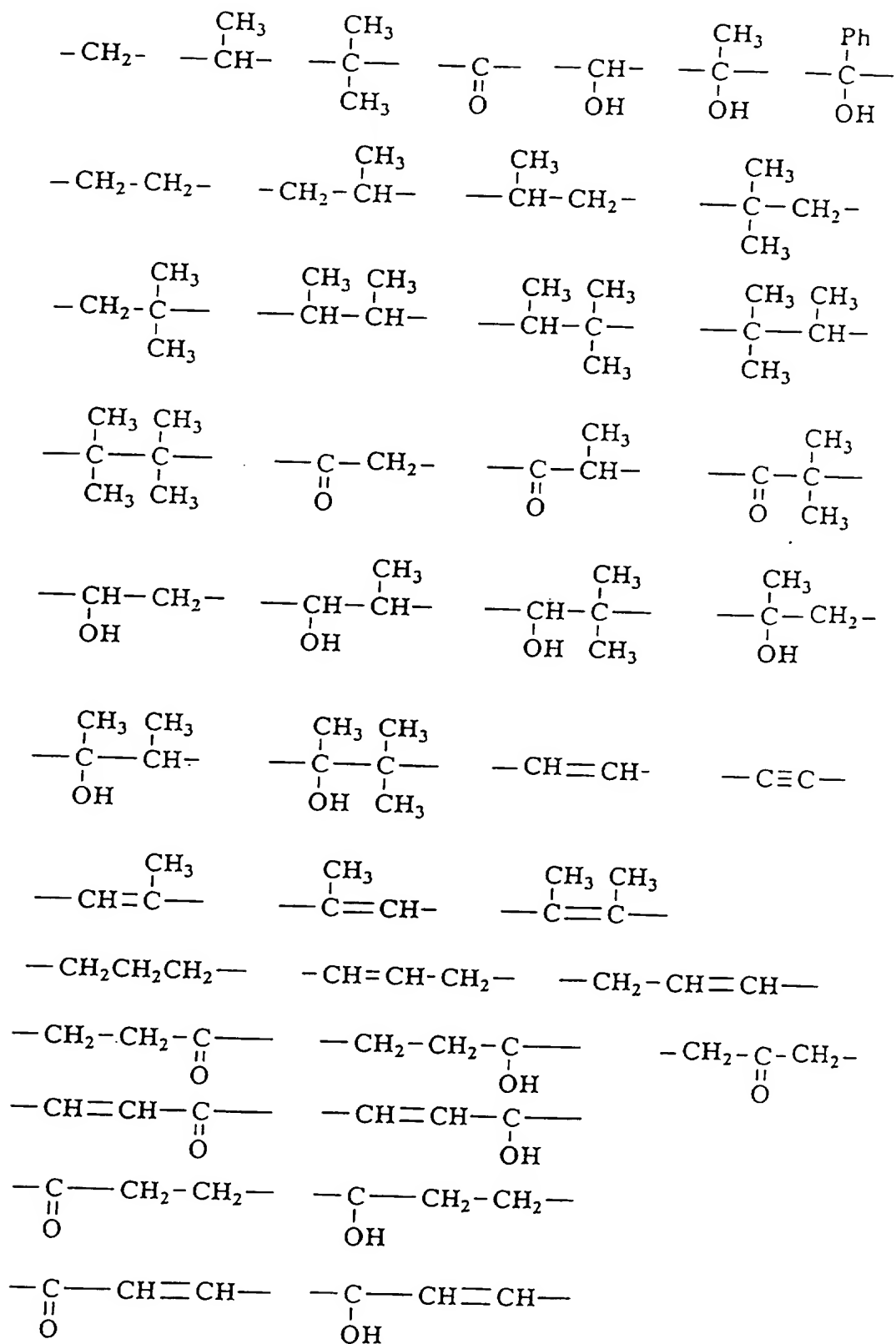
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wherein m is from 1 to 5, and each of R^d and R^e is independently a hydrogen atom, a methyl group or a
 20 hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d's together form a double bond, or adjacent R^d's and R^e's together form a triple bond.

(19) The indole type thiazolidine compound and its salt according to the above-mentioned (18), wherein:

25 R¹ is -W-Z, wherein W is



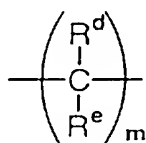
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(20) The indole type thiazolidine compound and its salt according to the above-mentioned (16), wherein:

R^1 is $-V-Z$, wherein V is S , SO or SO_2 .

(21) The indole type thiazolidine compound and its salt according to the above-mentioned (16), wherein:

R^1 is $-W-V-Z$, wherein W is



wherein m is from 1 to 5, and each of R^d and R^e is independently a hydrogen atom, a methyl group or a hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d 's together form a double bond, or adjacent R^d 's and R^e 's together form a triple bond (provided that R^d and R^e on the first carbon atom adjacent to N are not a hydroxyl group, and also provided that R^d and R^e on the first carbon atom adjacent to O are not hydroxyl groups or do not together form an oxo group), and

V is NR^8 (R^8 is a hydrogen atom or a C_1 - C_3 alkyl group).

(22) The indole type thiazolidine compound and its salt according to the above-mentioned (21), wherein:

R^1 is $-W-V-Z$, wherein $-W-V-$ is $-CO-NR^8-$ (R^8 is a hydrogen atom or a C_1 - C_3 alkyl group).

(23) The indole type thiazolidine compound and its salt according to the above-mentioned (8), (9), (11), (19), (20) or (21), wherein:

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Y is $-\text{CH}_2-$; and

R^4 is a hydrogen atom.

(24) The indole type thiazolidine compound and its salt according to the above-mentioned (8), (9), (11),
5 (19), (20) or (21), wherein: Y is CHR^7 (R^7 forms a bond together with R^4), and R^4 forms a bond together with R^7 .

The compound of the above formula (I) of the present invention has acidic hydrogen on a thiazolidine ring or on an oxazolidine ring. Further, when substituent Z is a
10 heterocyclic aromatic group or a heterocyclic aliphatic group, it sometimes has a basic nitrogen. Such a compound may be converted to a pharmaceutically acceptable non-toxic salt with an appropriate base or acid, if desired. The compound of the formula (I) can be
15 used for the purpose of the present invention either in the free form or in the form of a pharmaceutically acceptable salt. Examples of the basic salt include an alkali metal salt (lithium salt, sodium salt, potassium salt and the like), an alkali earth metal salt (calcium
20 salt, magnesium salt and the like), an aluminum salt, an ammonium salt which may be unsubstituted or substituted with a methyl, ethyl or benzyl group, an organic amine salt (methylamine salt, ethylamine salt, dimethylamine salt, diethylamine salt, trimethylamine salt,
25 triethylamine salt, cyclohexylamine salt, ethylenediamine salt, bicyclohexylamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, piperazine

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salt, dibenzylpiperidine salt, dehydroabietilamine salt, N,N'-bisdehydroabietilamine salt, benzathine(N,N'-dibenzylethylenediamine) salt, glucamine salt, meglumine(N-methylglucamine) salt, benetamine(N-benzylphenethylamine)salt, trometamine(2-amino-2-hydroxymethyl-1,3-propanediol)salt, choline salt, procaine salt), a basic amino acid salt (lysine salt, ornithine salt, arginine salt and the like), a pyridine salt, a collidine salt, a quinoline salt, and the like.

10 Examples of an acid-addition salt include a mineral acid salt (hydrochloride, hydrobromide, sulfate, hydrogensulfate, nitrate, phosphate, hydrogenphosphate, dihydrogenphosphate and the like), an organic acid salt (formate, acetate, propionate, succinate, malonate,

15 oxalate, maleate, fumarate, malate, citrate, tartrate, lactate, glutamate, asparate, picrate, carbonate and the like), a sulfonic acid salt (methanesulfonate, benzenesulfonate, toluenesulfonate and the like), and the like. Each of these salts can be prepared by a known

20 method.

The compound having the formula (I), i.e. indole type thiazolidines, can be prepared by the following synthetic methods.

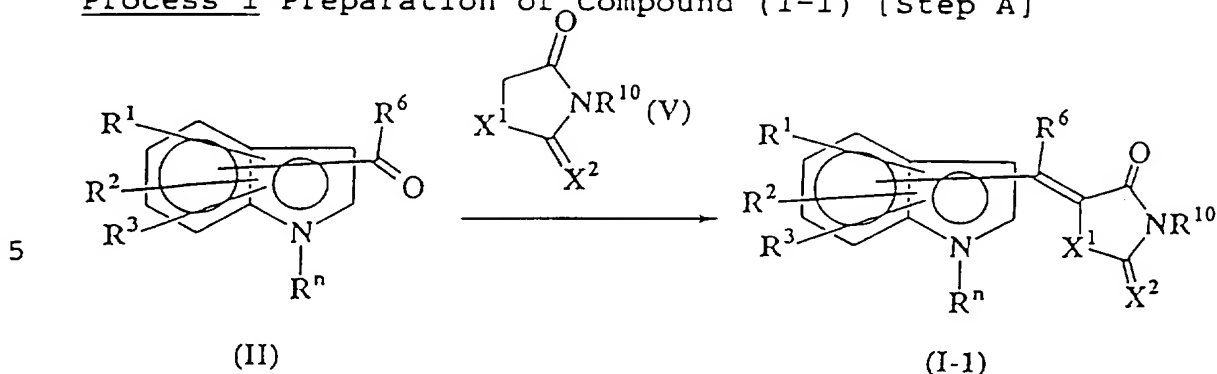
A reaction solvent used in the preparation is stable

25 under the reaction conditions, and is preferably so inert as not to inhibit the reaction. Examples of the reaction solvent include water, alcohols (such as methanol,

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ethanol, propanol, butanol and octanol), cellosolves (such as methoxyethanol and ethoxyethanol), aprotic polar organic solvents (such as dimethylformamide, dimethylsulfoxide, dimethylacetamide, tetramethylurea, 5 sulfolane and N,N-dimethylimidazolidinone), ethers (such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane), aliphatic hydrocarbons (such as pentane, n-hexane, c-hexane, octane, decaline and petroleum ether), aromatic hydrocarbons (such as benzene, chlorobenzene, 10 nitrobenzene, toluene, xylene and tetralin), halogenated hydrocarbons (such as chloroform, dichloromethane and dichloroethane), ketones (such as acetone, methyl ethyl ketone and methyl butyl ketone), lower aliphatic acid esters (such as methyl acetate, ethyl acetate and methyl 15 propionate), alkoxy alkanes (such as dimethoxyethane and diethoxyethane), acetonitrile, and the like. These solvents are optionally selected depending on the reactivity of the aimed reaction, and are respectively used alone or in a mixture. In some cases, there are 20 used as an anhydrous solvent by using a dehydrating agent or a drying agent. The above-mentioned solvents are merely examples which can be used in the reaction of the present invention, and the present invention is not limited to these conditions.

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Process 1 Preparation of Compound (I-1) [Step A]

(wherein R^1 , R^2 , R^3 , R^6 , R^n , X^1 and X^2 are as defined above, and R^{10} is a hydrogen atom or a protecting group of amide (such as Tr: trityl)).

10

A compound wherein R^4 and R^7 are bonded together in the formula (I), i.e. a compound of the formula (I-1), can be obtained by dehydration-condensation of a compound of the formula (II) and a compound of the formula (V).

15 The compound of the formula (II) is a well known compound or can be synthesized by the method disclosed in Japanese Unexamined Patent Publication No. 271288/1991, Japanese Unexamined Patent Publication No. 277660/1988, Japanese Unexamined Patent Publication No. 71321/1975 or Japanese

20 Examined patent Publication No. 34986/1974. The compound of the formula (V) is a well known compound or can be synthesized by the method disclosed in "J. Prakt. Chem." (vol. 2, p. 253, 1909), "J. Prakt. Chem." (vol. 3, p. 45, 1919), "Chem. Ber." (vol. 118, p. 774, 1985), and German

25 Laid Open Patent Publication No. DE-3045059. The compound of the formula (V) wherein R^{10} is hydrogen, can be used in this reaction after displacing its acidic

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hydrogen at the 3-position of thiazolidine or oxazolidine with an appropriate substituent (such as TR: trityl) by a well known method.

This reaction is conducted usually in an appropriate organic solvent in the presence of base or acid.

Examples of such a solvent include alcohols, cellosolves, aprotic polar organic solvents, ethers, aromatic hydrocarbons, halogenated hydrocarbons, alkoxyalkanes and acetonitrile.

Examples of the base and the acid include organic amines (such as dimethylamine, diethylamine, diisopropylamine, diisopropylethylamine, trimethylamine, triethylamine, piperidine, piperazine, pyrrolidine, morpholine, pyridine, methanolamine and ethanolamine),
Acid Capture H: 3,4-dihydro-2H-pyrid[1,2-a]pyrimidin-2-one, Acid Capture 9M: 9-methyl-3,4-dihydro-2H-pyrid[1,2-a]pyrimidin-2-one, and the like, or metal alkoxides (such as sodium methoxide, sodium ethoxide, lithium isopropoxide and potassium t-butoxide), inorganic alkali metal salts (such as potassium carbonate, sodium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydride, potassium hydride, calcium hydride, sodium acetate and potassium acetate), organic acids (such as acetic acid, trichloroacetic acid and trifluoroacetic acid), inorganic acids (such as phosphoric acid), and the like. These materials are selected appropriately depending on the reactivity of the

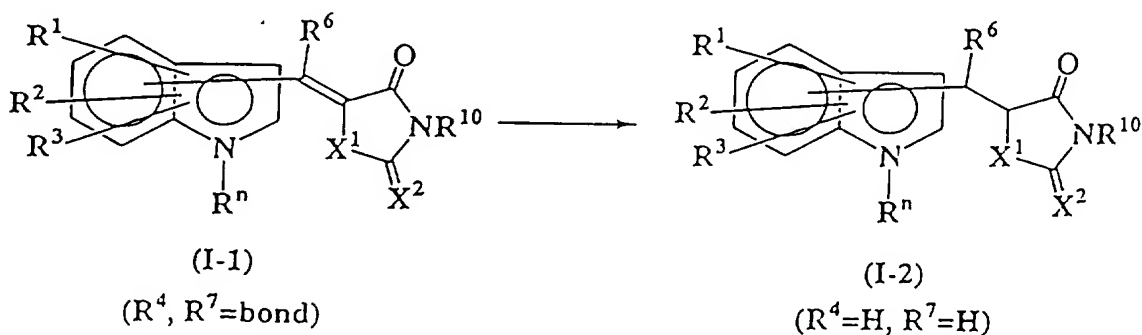
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aimed reaction.

This reaction can be accelerated by removing water formed during the reaction out of the system by using an appropriate dehydrating agent such as molecular sieves
 5 and anhydrous sodium sulfate or by azeotropic distillation using Dean-Stark tube.

This reaction is conducted usually at a temperature ranging from 0°C to a boiling point of a solvent used, preferably from 20°C to 120°C, for from 0.5 to 30 hours.

10 Process 2 Preparation of Compound (I-2) [Step B]



(wherein R¹, R², R³, R⁶, R¹⁰, Rⁿ, X¹ and X² are as defined above).

20 A compound of the formula (I-1) (R⁴ and R⁷ together form a bond) obtained by the above method can be converted into a compound of the formula (I-2) (R⁴ and R⁷=H) in accordance with an appropriate reduction method, for example by catalytically hydrogenating in the
 25 presence of an appropriate catalyst, or by using an appropriate metal-hydrogen complex compound, or by reducing a double bond connecting an indole ring with a

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thiazolidine or oxazolidine ring in a lower alcohol such as methanol by magnesium or sodium amalgam.

The reduction reaction by catalytic hydrogenation is conducted usually in a solvent such as water, alcohols, cellosolves, aprotic polar organic solvents, ethers, 5 alkoxyalkanes, lower aliphatic acid esters or lower aliphatic acids, preferably water, methanol, ethanol, methoxyethanol, dimethylformamide, dimethylacetamide, tetrahydrofuran, dioxane, dimethoxyethane, ethylacetate 10 or acetic acid. The solvent may be used alone or in a mixture. Examples of the catalyst used in this reaction include Raney nickel, palladium black, palladium carbon, ruthenium carbon, platinum oxide and the like. This reaction proceeds usually at normal temperature and a 15 atmospheric pressure but it is preferable for accelerating the procedure of the reaction to optionally employ an elevated temperature and a higher pressure.

In the case of the reduction reaction using a metal-hydrogen complex compound, a reaction is conducted in 20 water or an appropriate organic solvent at a temperature of from 0°C to 150°C, preferably from 0°C to 30°C, and examples of the metal-hydrogen complex compound include sodium borohydride, potassium borohydride, lithium borohydride, sodium cyanoborohydride, potassium tri-s- 25 butylborohydride, potassium triethylborohydride, lithium triethylborohydride, sodium triethylborohydride, tetramethylammonium borohydride, tetra-n-butylammonium

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borohydride, tetra-n-butylammonium cyanoborohydride, sodium triacetoxyborohydride, tetra-n-butylammonium triacetoxyborohydride, lithium t-hexylborohydride, potassium triphenylborohydride, sodium

5 trimethoxyborohydride, rhodium borohydride, tetraethylammonium borohydride, methyltrioctylammonium borohydride, calcium borohydride bis(tetrahydrofuran), lithium dimethylborohydride, zinc borohydride and the like. Also, in this reduction, an undesired side

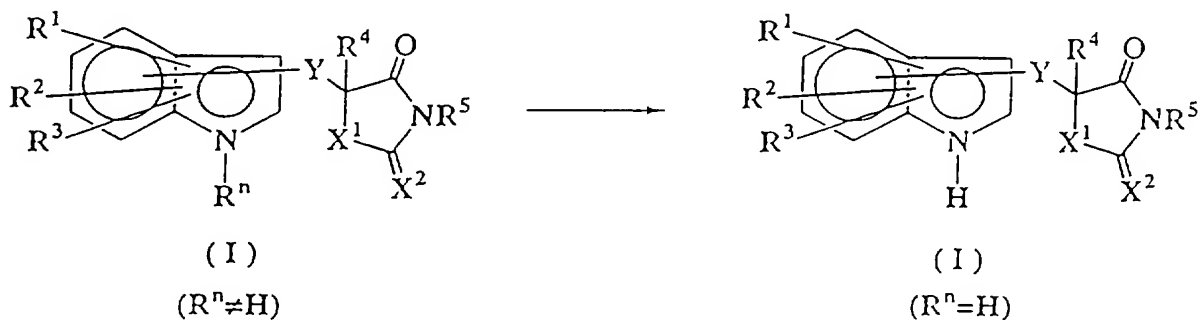
10 reaction can be inhibited by adding a Co reagent such as CoCl_2 , CoCl_3 and Co(OAc)_2 in the presence of a ligand such as dimethyl glyoxime, 2,2'-dipyridyl and 1,10-phenanthroline (see WO 93/13095).

In the case of the reduction using an amalgam, the

15 reaction is conducted in a solvent such as alcohols, preferably ethanol or ethanol at a temperature of from -20°C to a boiling point of a solvent used, preferably from 0°C to 50°C . Also, the reduction method by magnesium/methanol can be employed, as described in "J.

20 Org. Chem.", vol. 40, P 127 (1975).

Process 3 Preparation of Compound (I) (Displacement of substituent R^n) [Step C]



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(wherein R^1 , R^2 , R^3 , R^4 , R^5 , X^1 , X^2 and Y are as defined above, R^n is a substituent (other than a hydrogen atom) at the 1-position of an indole ring).

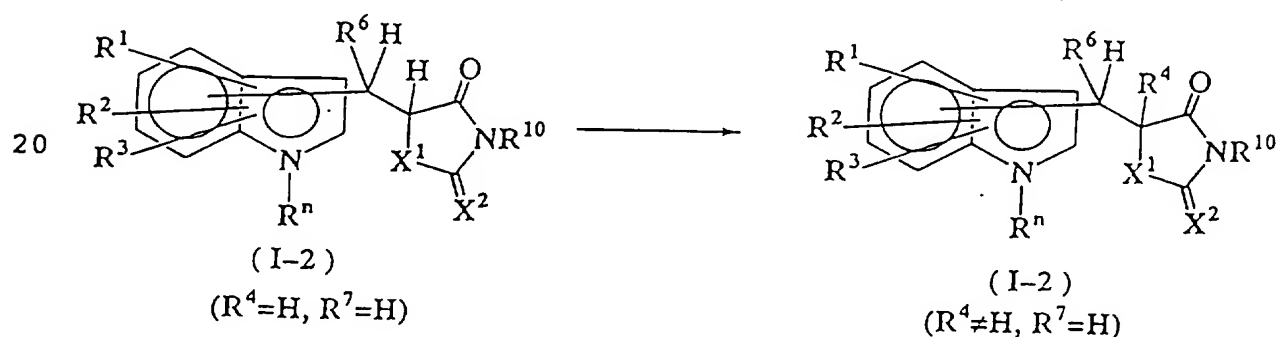
Among the compounds of the formula (I), the R^n substituent other than a hydrogen atom at the 1-position of an indole ring can be converted to a hydrogen atom by a well known appropriate method. The following reaction conditions can be employed depending on the type of the substituent R^n .

10 The displacement of the R^n substituent can be conducted by heat-refluxing for 1 to 12 hours in a mixture solution of sodium hydroxide aqueous solution/ethanol when R^n is a benzenesulfonyl group, a p-toluenesulfonyl group or a p-methoxybenzenesulfonyl group; by catalytically reducing in the presence of
15 palladium carbon, lithium aluminum hydride or Raney nickel in methanol, ethyl acetate or tetrahydrofuran when R^n is a methoxy group, a methoxymethyloxy group, a methoxyethyloxy group or a benzyloxymethyloxy group; by
20 stirring at room temperature in trifluoroacetic acid, a mixture solution of sodium hydroxide/methanol or a mixture solution of hydrochloric acid aqueous solution/methanol when R^n is a tertiary butylamino carbonyl group or a tertiary butoxy carbonyl group; by
25 using tetra-n-butylammonium fluoride or cesium fluoride in tetrahydrofuran at room temperature when R^n is a trimethylsilyl group, a tertiary butyldimethylsilyl

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group, a tertiary butyldiphenylsilyl group or a triisopropylsilyl group; by stirring at room temperature in a mixture solution of sodium hydroxide aqueous solution/ethanol when R^n is an acetyl group or a trifluoroacetyl group; by using tetrabutylammonium fluoride or a cesium fluoride at room temperature in tetrahydrofuran when R^n is a trimethylsilylethyloxymethyl group; by using lithium bromide and boron trifluoride/ether complex and acetic anhydride when R^n is a methoxymethyl group; by using sodium methoxide or sodium borohydride in methanol at room temperature when R^n is a dimethylaminomethyl group; or by heating at 80°C to 200°C and decarboxylating when R^n is a carboxyl group, thus converting the substituent at the 1-position to a hydrogen atom.

Process 4 Displacement of R^4 substituent of Compound (I-2) [Step D]



(wherein $R^1, R^2, R^3, R^4, R^6, R^{10}, X^1$ and X^2 are as defined above).

A compound of the formula (I-2) ($R^4, R^7=H$) can be

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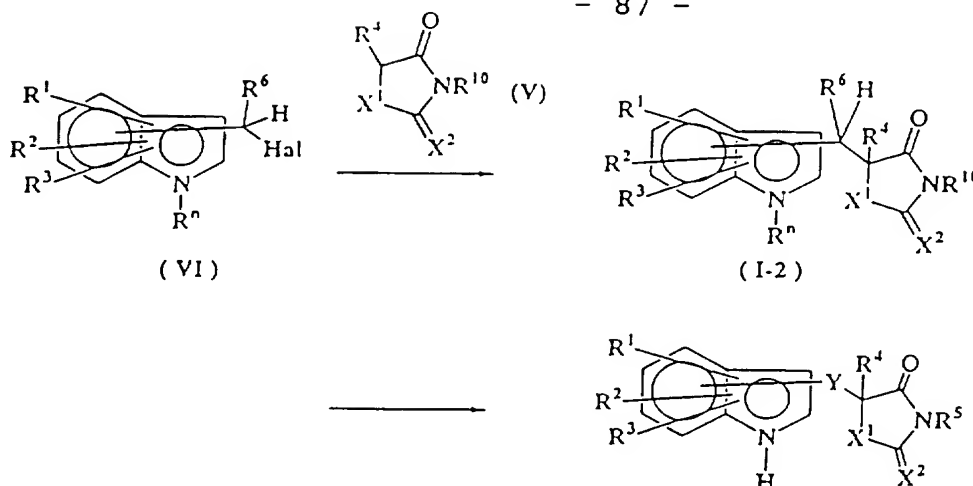
converted into a compound of the formula (I-2) ($R^4 \neq H$, $R^7 = H$) in accordance with a well known method by alkylating hydrogen at the 5-position of a thiazolidine or oxazolidine ring with an appropriate alkylating agent
5 (such as alkylhalides including methyl iodide and ethyl iodide, alkylsulfates including dimethylsulfate and diethylsulfate, or aliphatic or aromatic sulfonic acid esters including methyltosylate and methylmesylate).

This reaction is conducted usually in the presence of
10 a base in an appropriate organic solvent. Examples of the solvent used include aprotic polar organic solvents, ethers, and alkoxy alkanes, preferably tetrahydrofuran and dimethoxy ethane. Examples of the base include alkali metal amides (such as LDA: lithium diisopropyl
15 amide and potassium amide), aliphatic or aromatic lithium compounds (such as n-butyl lithium, t-butyl lithium and phenyl lithium), and the like. These materials are selected optionally depending on the reactivity of the aimed reaction.

20 This reaction is conducted usually at a temperature in the range of from -20°C to 100°C , preferably from -10°C to 30°C for 0.1 to 10 hours.

Process 5 Preparation of Compound (I-2) [Step E] and Deprotection of R^{10}

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(wherein R^1 , R^2 , R^3 , R^4 , R^6 , R^{10} , R^n , X^1 and X^2 are as
 10 defined above, and R^{12} is an appropriate leaving group in
 nucleophilic displacement in the present reaction,
 examples of which include a halogen such as chloro, bromo
 and iodo, and an aromatic or aliphatic sulfonyloxy group
 such as p-toluenesulfonyloxy, benzenesulfonyloxy and
 15 methanesulfonyloxy).

A compound of the formula (I) other than the one
 wherein R^4 and R^7 together form a bond, i.e. a compound
 of the formula (I-2), can be obtained by reacting a
 compound of the formula (V) with an indole derivative of
 20 the formula (VI). The compound of the formula (V) used
 herein is a well known compound or can be synthesized by
 a method disclosed in "Ukr. Khim. Zh." (vol. 16, p. 545,
 1950), "J. Med. Chem." (vol. 34, p. 1538, 1991), "J.
 Prakt. Chem." (vol. 2, 79, P. 259 (1909), "J. Prakt.
 25 Chem." (vol. 2, 99, P. 56 (1919) or Japanese Unexamined
 Patent Publication No. 216882/1984. The compound of the
 formula (V) wherein R^{10} is hydrogen, is used in this

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reaction preferably after displacing its acidic hydrogen with an appropriate substituent (such as Tr: trityl) by a known method.

This reaction is conducted usually in an appropriate organic solvent in the presence of base. Examples of the solvent thus used include aprotic polar organic solvents (such as HMPA: hexamethylphosphoric triamide and DMPU: 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidine), ethers (such as THF: tetrahydrofuran) and alkoxyalkanes, and the solvent may be used respectively alone or in a mixture. Examples of the base thus used include a strong base such as alkali metal amides (e.g. LDA: lithium diisopropyl amide, sodium amide and potassium amide) and aliphatic or aromatic lithium compounds (e.g. n-butyl lithium, t-butyl lithium and phenyl lithium). These materials are selected optionally depending on the reactivity of the aimed reaction.

The reaction using a compound of the formula (V) wherein R^4 and R^{10} are hydrogen, can be conducted in accordance with a method disclosed in "J. Labelled Compounds and Radiopharmaceuticals" (vol. XXVIII, No. 8, p. 911, 1990). In such a case, a compound of the formula (V) is reacted with n-butyl lithium usually in an inert gas atmosphere such as nitrogen and in a mixed solvent such as THF: HMPA=4:1 at a temperature of from -100°C to -10°C to form an anion, which is then reacted with an indole compound of the formula (VI) to obtain a compound

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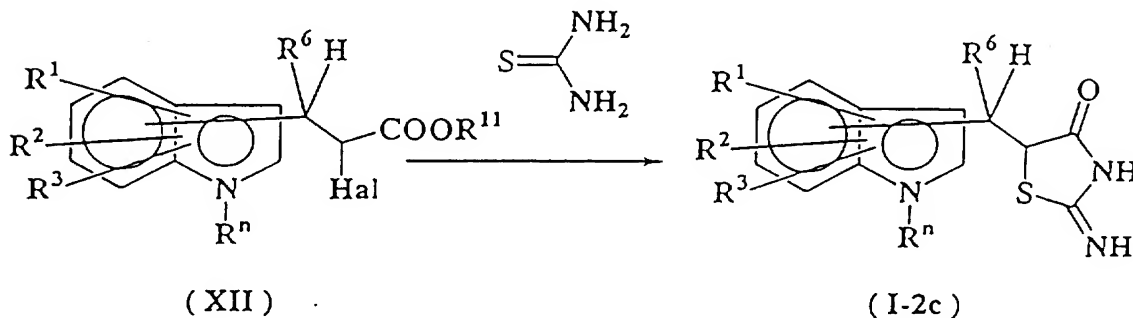
of the formula (I-2). The reaction of the anion and the indole compound (VI) is conducted usually at a temperature of from -50°C to 100°C, preferably from -10°C to room temperature. The reaction time may be varied
5 depending on the materials used, but is usually from 0.5 to 1 hour for the formation of an anion and from 0.5 to 5 hours for the reaction with an indole compound.

Also, this reaction can be conducted in accordance with a method disclosed in "J. Amer. Chem. Soc." (vol.
10 87, p. 4588, 1965) or "J. Med. Chem." (vol. 34, p. 1538, 1991). In such a case, a compound of the formula (V) is reacted with magnesium methylcarbonate in an inert gas atmosphere such as nitrogen and in an aprotic polar organic solvent such as dimethylformamide to form a
15 chelate compound, and the chelate compound thus formed is further reacted with an indole compound of the formula (VI) to obtain a compound of the formula (I-2). This reaction is conducted usually at a temperature ranging from 20°C to 150°C, preferably from 70°C to 100°C. The
20 reaction time varies depending on the materials used, but the formation of the chelate compound takes from 0.5 to 2 hours and the reaction with the indole compound takes from 0.5 to 5 hours.

In some cases, an amide group at the 3-position of
25 thiazolidine ring of the compound of the formula (I-2) thus obtained may be deprotected by a well-known method. When R¹⁰ is Tr (trityl), this method is conducted by

using an organic acid such as trifluoroacetic acid and trichloroacetic acid or an inorganic acid such as hydrochloric acid and sulfuric acid. This reaction is conducted in the absence of a solvent or in the presence of a solvent such as ethers including tetrahydrofuran and dioxane and halogenated solvents including chloroform and dichloromethane, at a temperature ranging from 0°C to 100°C, preferably from 10°C to 50°C, for 0.1 to 5 hours.

Process 6



15

(wherein R¹, R², R³ and R⁶ are as defined above, and R¹¹ is C₁-C₄ alkyl such as methyl, ethyl, n-propyl, i-propyl, n-butyl and t-butyl, and Hal is a halogen atom such as a chlorine atom, a bromine atom and an iodide atom).

20 A compound of the formula (I) wherein R^4 and R^7 are H and X^1 is S and X^2 is NH, i.e. a compound of the formula (I-2c) ($R^4, R^7=H, X^1=S, X^2=NH$), can be obtained by reacting thiourea with a halocarboxylic acid ester of the formula (XII).

25 This reaction is conducted usually in an appropriate organic solvent in the presence of base or acid. Examples of the solvent used include alcohols,

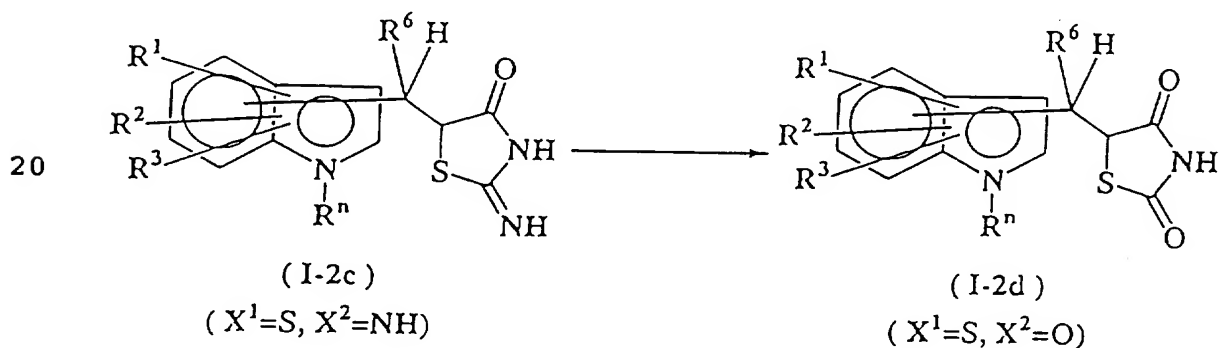
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cellosolves and aprotic polar organic solvents,
preferably sulfolane.

This reaction is conducted at a temperature of from
0°C to a boiling point of a solvent used, preferably from
5 50°C to 150°C, for 0.5 to 10 hours.

As the reaction proceeds, a hydrogen halide is by
produced, but the reaction can be accelerated by
capturing the by-produced hydrogen halide with an
appropriate base. Examples of the base used include
10 organic amines (such as dimethylamine, diethylamine,
diisopropylamine, diisopropylethylamine, trimethylamine,
triethylamine, piperidine, piperazine, pyrrolidine,
morpholine, pyridine, methanolamine and ethanolamine),
inorganic alkali metal salts (such as sodium acetate and
15 potassium acetate) and the like.

Process 7



(wherein R¹, R², R³, R⁶ and Rⁿ are as defined above).

25 A compound of the formula (I-2c) (X¹=S, X²=NH), can
be converted into a compound of the formula (I-2d) (X¹=S,
X²=O) by hydrolyzing an imino group at the 2-position of

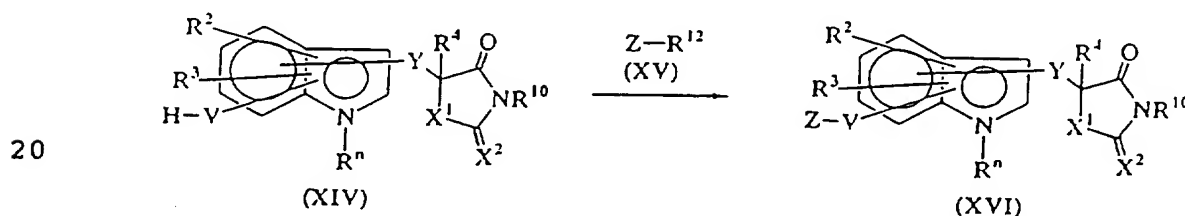
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thiazolidine by a well known method.

This reaction is conducted usually in the presence of water and an acid in an appropriate organic solvent. Examples of the solvent include usually alcohols, cellosolves, aprotic polar organic solvents, ethers and alkoxy alkanes, preferably methanol, ethanol, methoxyethanol, sulfolane, dioxane and dimethoxyethane. Examples of the acid include inorganic acids (such as hydrochloric acid, sulfuric acid and hydrobromic acid), and these materials are selected optionally depending on the reactivity of the aimed reaction.

This reaction is conducted usually at a temperature in the range of from 50°C to a boiling point of a solvent used in the reaction, preferably from 80°C to 150°C. The reaction time is usually from 0.5 to 30 hours.

Process 8



(wherein R^2 , R^3 , R^4 , R^{10} , R^{12} , X^1 , X^2 , Y , V and Z are as defined above).

An indole compound ($R^1 = -V-Z$) of the formula (XVI) can also be obtained by reacting a compound of the formula (XV) with a hydroxyl group, a thiol group or an amino group of an indole compound of the formula (XIV) by a

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nucleophilic substitution reaction. The compound of the formula (XIV) is preferably protected by substituting hydrogen of R¹⁰ with an appropriate substituent (such as Tr: trityl).

- 5 This reaction is usually conducted in an appropriate organic solvent in the presence of base. Examples of the solvent used include aprotic polar organic solvents, ethers, aromatic hydrocarbons, hydrogenated hydrocarbons, alkoxyalkanes, acetonitrile, and the like.
- 10 Examples of the base thus used include organic amines (such as dimethylamine, diethylamine, diisopropylamine, diisopropylethylamine, trimethylamine, triethylamine, piperidine, piperazine, pyrrolidine, morpholine, pyridine, methanolamine and ethanolamine), Acid Captor H:
- 15 3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one and Acid Captor 9M: 9-methyl-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one), metal alkoxides (such as sodium methoxide, sodium ethoxide, lithium isopropoxide and potassium t-butoxide), inorganic alkali metal salts (such
- 20 as sodium hydroxide, potassium hydroxide, lithium hydroxide, potassium carbonate, sodium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydride, sodium acetate and potassium acetate), and alkali metal amides (such as sodium amide). These
- 25 materials are selected appropriately depending on the reactivity of the aimed reaction.

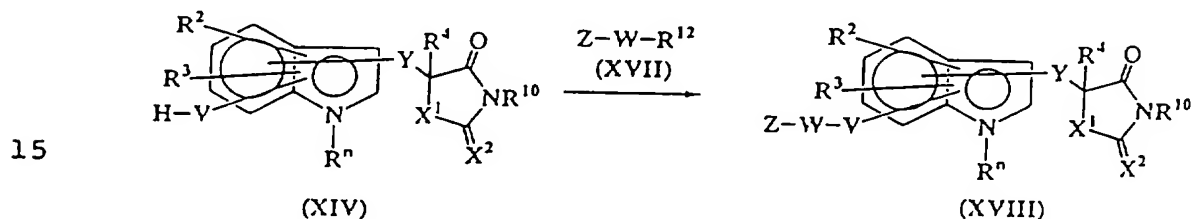
This reaction is conducted usually at a temperature

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ranging from -20°C to a boiling point of the solvent used, preferably from 20°C to 150°C, for from 0.5 to 30 hours.

Among compounds thus obtained, the one having a
 5 protecting group on the thiazolidine ring as represented by the formula (XVI), can be led to a compound of the formula (I) either in accordance with the method disclosed by T.W. Greene, P.G.M. Wuts in "Protective
 Groups in Organic Synthesis" (1991) or deprotecting the
 10 amide group at the 3-position of the thiazolidine ring by the method described in Process 5.

Process 9



(wherein R^2 , R^3 , R^4 , R^{10} , R^{12} , R^n , X^1 , X^2 , Y , V , W and Z are as defined above).

An indole compound ($R^1 = -V-W-Z$) of the formula
 20 (XVIII), can also be obtained by reacting a compound of the formula (XVII) with a hydroxyl group, a thiol group or an amino group of an indole compound of the formula (XIV) by nucleophilic substitution reaction. The compound of the formula (XIV) is preferably protected by
 25 substituting hydrogen of R^{10} with an appropriate substituent (such as Tr: trityl).

Among compounds of the formula (I), a compound

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wherein R^1 is -V-W-Z and W is COCH_2 , can be obtained by using a compound of $\text{Z-COCH}_2\text{-Hal}$ ($\text{W}=\text{COCH}_2$, $\text{R}^{12}=\text{Hal}$, Z and Hal are substituents explained above). Such a compound is well known and is commercially available, or can be

5 obtained by a well known method (for example, British Laid Open Patent Publication No. 1107677 discloses a compound wherein Z is pyrrole, Japanese Unexamined Patent Publication No. 85372/1986 discloses a compound wherein Z is oxazole or thiazole and U.S. Patent No. 4,167,626

10 discloses a compound wherein Z is triazole). Also, such a compound can be obtained by halogenating Z-COCH_3 (for example, "Bull. Soc. Chim. Fr., p. 1760 (1973)" discloses a compound wherein Z is furan, "Tetrahedron, 29(2), p. 413 (1973)" discloses a compound wherein Z is thiophene,

15 "J. Heterocyclic Chem., 27(5), p. 1209 (1990)" discloses a compound wherein Z is pyrrole, "Bull. Soc. Chim. Fr., p. 540 (1988)", "Bull. Soc. Chim. Fr., p. 318 (1987)", "J. Heterocyclic Chem., 23(1), P. 275 (1986)", "Arch. Pharm., 316(7), p. 608 (1983)" and "Synlett., (7), p. 483

20 (1991)" disclose a compound wherein Z is pyrazole, "J. Heterocyclic Chem., 17(8), p. 1723 (1980)" discloses a compound wherein Z is imidazole, and "J. Chem. Soc. C(20), p. 2005 (1976)" and "Heterocycles, 26(3), p. 745 (1987)" disclose a compound wherein Z is triazole) as a

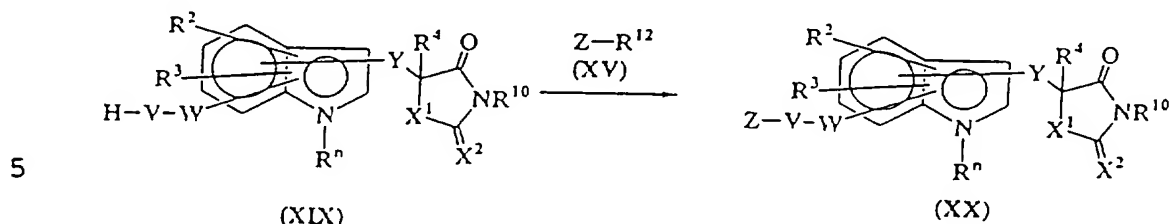
25 starting material by means of an appropriate well known halogenation method (e.g. a method disclosed in Japanese Unexamined Patent Publication No. 85372/1986). Also,

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such a compound can be obtained by subjecting Z-CO₂R' (R'=lower alkyl or substituted or unsubstituted benzyl) (for example, "Z. Chem., 9(1), p. 22 (1969)" and "Synth. Commun., 20(16), p. 2537 (1990)" disclose a compound
5 wherein Z is thiophene, "J. Org. Chem., 55(15), p. 4735 (1990)" and "Chem. Pharm. Bull., 17(3), p. 582 (1969)" disclose a compound wherein Z is pyrrole, European Laid Open Patent Publication No. 506194 discloses a compound wherein Z is imidazole, and "Chem. Ber., 117(3), p. 1194
10 (1984)" discloses a compound wherein Z is pyrazole or triazole) as a starting material to an appropriate well known reduction-oxidation reaction (for example, reduction by diisobutyl aluminum hydride and then oxidation by manganese dioxide) to obtain Z-CHO, and
15 further by converting the product thus obtained to Z-COCH₂-hal by an appropriate method (e.g. a method disclosed in "Tetrahedron Letters, p. 4661 (1972)").

This reaction can be conducted in the same manner as in the Process 8.

20 Among compounds thus obtained, the one having a protecting group on the thiazolidine ring as represented by the formula (XVIII), can be led to a compound of the formula (I) either in accordance with the method disclosed by T.W. Greene, P.G.M. Wuts in "Protective
25 Groups in Organic Synthesis" (1991) or deprotecting the amide group at the 3-position of the thiazolidine ring by the method described in Process 5.

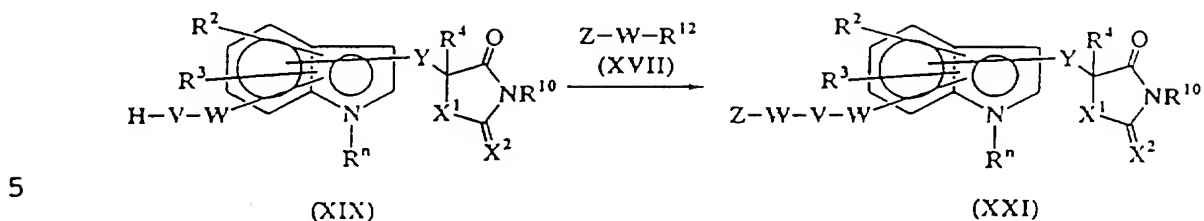
Process 10

(wherein R^2 , R^3 , R^4 , R^{10} , R^{12} , R^n , X^1 , X^2 , Y , V , W and Z are as defined above).

10 An indole compound ($R^1 = -W-V-Z$) of the formula (XX) can also be obtained by reacting a compound of the formula (XV) with a hydroxyl group, a thiol group or an amino group of an indole compound of the formula (XIX) by nucleophilic substitution. The compound of the formula
15 (XIX) is preferably protected by substituting hydrogen of R^{10} with an appropriate substituent (such as Tr: trityl).

This reaction can be conducted in the same manner as in the above Process 8.

Among the compounds thus obtained, the compound
20 having a protective group introduced into a thiazolidine ring part of the formula (XX) can be converted into a compound of the formula (I) by deprotecting an amino group at the 3-position of the thiazolidine ring in accordance with the method disclosed by T.W. Greene,
25 P.G.M. Wuts "Protective Groups in Organic Synthesis" (1991) or the method disclosed in the Process 5.

Process 11

(wherein R^2 , R^3 , R^4 , R^{10} , R^{12} , R^n , X^1 , X^2 , Y , V , W and Z are as defined above).

An indole compound ($R^1 = -W-V-W-Z$) of the formula (XXI) can also be obtained by reacting a compound of the formula (XVII) with a hydroxyl group, a thiol group or an amino group of an indole compound of the formula (XIX). The compound of the formula (XIX) is preferably protected by substituting hydrogen of R^{10} with an appropriate substituent (such as Tr: trityl).

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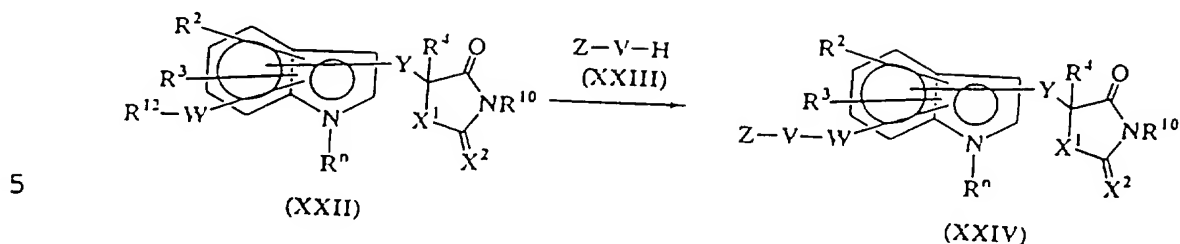
This reaction can be conducted in the same manner as in the above Process 8.

Among the compounds thus obtained, the compound having a protective group introduced into a thiazolidine ring part of the formula (XXI) can be converted to a compound of the formula (I) by deprotecting an amino group at the 3-position of the thiazolidine ring in accordance with the method disclosed by T.W. Green, P.G.M. Wuts "Protective Groups in Organic Synthesis" (1991) or the method disclosed in the above Process 5.

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Process 12

(wherein R^2 , R^3 , R^4 , R^{10} , R^{12} , R^n , X^1 , X^2 , Y , V , W and Z are as defined above).

An indole compound ($R^1 = -W-V-Z$) of the formula (XXIV) can also be obtained by reacting an indole compound of the formula (XXII) with a hydroxyl group, a thiol group or an amino group of a compound of the formula (XXIII) by nucleophilic substitution. The compound of the formula (XXII) is preferably protected by substituting hydrogen of R^{10} with an appropriate substituent (such as Tr: trityl).

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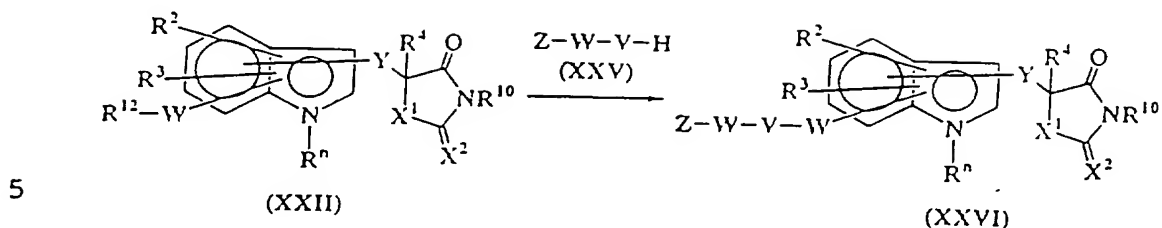
This reaction can be conducted in the same manner as in the above Process 8.

Among the compounds thus obtained, a compound having a protective group introduced into a thiazolidine ring part of the formula (XXIV) can be converted to a compound of the formula (I) by deprotecting an amino group at the 3-position of the thiazolidine ring in accordance with the method disclosed by T.W. Greene, P.G.M. Wuts "Protective Groups in Organic Synthesis" (1991) or the method disclosed in the above Process 5.

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Process 13

(wherein R^2 , R^3 , R^4 , R^{10} , R^{12} , R^n , X^1 , X^2 , Y , V , W and Z are as defined above).

An indole compound ($R^1 = -W-V-W-Z$) of the formula
 10 (XXVI) can also be obtained by reacting an indole compound of the formula (XXII) with a hydroxyl group, a thiol or an amino group of a compound of the formula (XXV). The compound of the formula (XXII) is preferably protected by substituting hydrogen of R^{10} with an
 15 appropriate substituent (such as Tr: trityl).

This reaction can be conducted in the same manner as in the above Process 8.

Among the compounds thus obtained, a compound having a protective group introduced into a thiazolidine ring
 20 part of the formula (XXVI) can be converted to a compound of the formula (I) by deprotecting an amino group at the 3-position of the thiazolidine ring in accordance with the method disclosed by T.W. Greene, P.G.M. Wuts "Protective Groups in Organic Synthesis" (1991) or the
 25 method disclosed in the above Process 5.

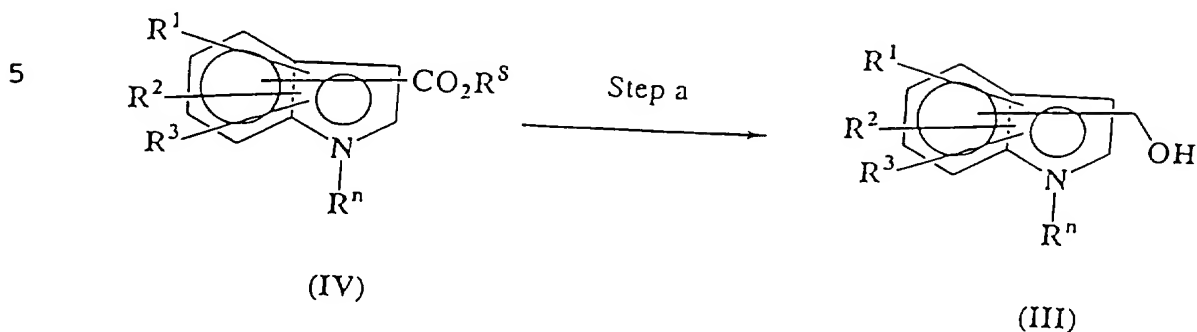
Now, the processes for producing intermediates useful for the preparation of the compounds of the present

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invention will be described hereinafter.

Method for preparing intermediate (III)

Synthesis Route 1 [Step a]



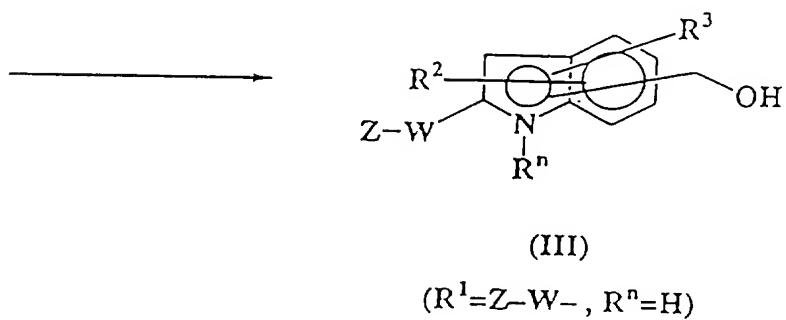
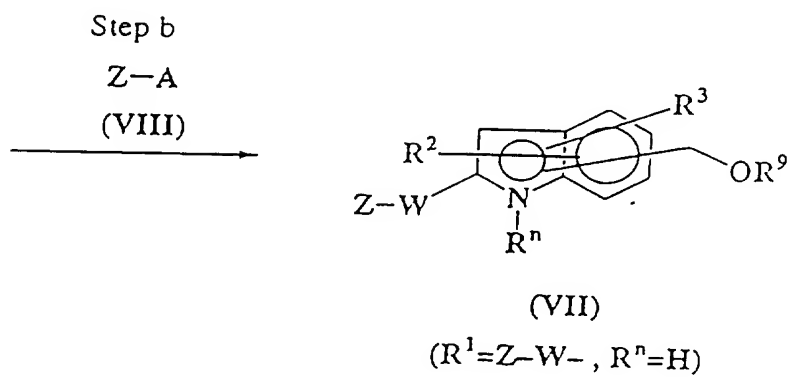
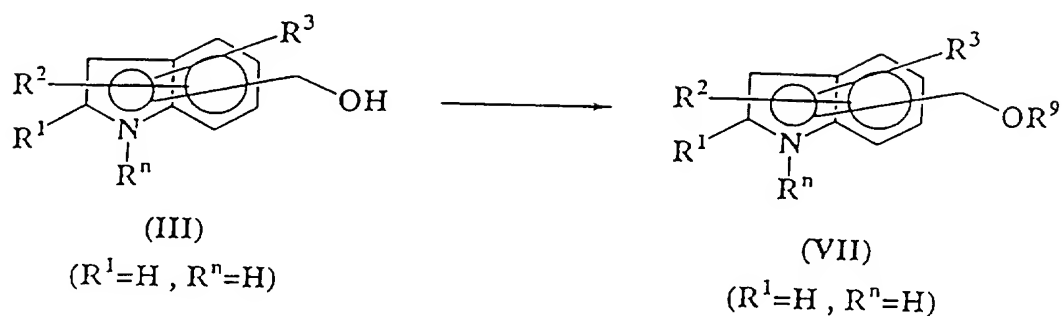
10 (wherein R^1 , R^2 , R^3 and R^n are as defined above, and R^8 is a hydrogen atom, a C_1 - C_4 alkyl group, a phenyl group or a benzyl group).

A hydroxymethylindole (intermediate (III)) is available by using a commercial available reagent or by
 15 reducing a carboxyl indole of the formula (IV) or an alkoxycarbonylindole.

The step of synthesizing the compound of the formula (III) can be conducted by using a well known appropriate reducing agent (e.g. metal hydride complex compounds such
 20 as LAH: lithium aluminum hydride, SAH: sodium aluminum hydride, sodium triethoxyaluminum hydride, Red-Al: sodium bis(2-methoxyethoxy) aluminum hydride, SBH: sodium borohydride and LBH: lithium borohydride, and metal hydride compounds such as DIBAH: diisobutyl aluminum
 25 hydride, and catalytic hydrogenation using CuBaCrO as a catalyst).

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Synthesis Route 2 Introduction of substituent R^1 into the 2-position of indole



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(wherein R^1 , R^2 , R^3 , R^n , W and Z are as defined above, and R^9 is a protecting group (such as t-butyldimethylsilyl group) of a primary hydroxymethyl group).

5 Among hydroxymethyl indole compounds of the formula (III), a compound having a hydrogen atom at the 2-position of an indole ring can get a carbon functional group: R^1 (Z-W-, Z-V-W-, Z-W-V- and Z-V-) introduced at the 2-position by means of the following method.

10 (Protection of hydroxymethyl group)

 In this synthesis route, a compound (VII) can be obtained by protecting a primary hydroxymethyl group of hydroxymethyl indole of the formula (III) by means of a well known method. For example, protection of these
15 alcohols can be conducted in accordance with the method disclosed by T.W. Greene, P.G M. Wuts in " Protective Groups in Organic Synthesis" (1991). A protective group: R^9 is preferably stable under basic conditions in the following step, examples of which include a substituted
20 silyl group (such as trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylthexylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, tribenzylsilyl, tri-p-xylylsilyl, triphenylsilyl, diphenylmethylsilyl and
25 t-butylmethoxyphenylsilyl), a substituted acyl group (such as chloroacetyl, dichloroacetyl, trichloroacetyl, fluoroacetyl, difluoroacetyl, trifluoroacetyl and

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pivaloyl), benzoyl, a substituted alkoxy carbonyl group (such as methoxycarbonyl, ethoxycarbonyl, t-butyloxycarbonyl and i-butyloxycarbonyl), and the like, particularly preferably triisopropylsilyl, t-butyl-
5 butyldimethylsilyl, t-butyl diphenylsilyl and the like. When the protective group is t-butyl dimethylsilyl, this reaction is conducted by using t-butyl dimethylsilyl chloride in dimethylformamide in the presence of imidazole at room temperature in accordance with J. Amer.
10 Chem. Soc., vol. 94, P 6190 (1972).
(Step b)

In Step b, at the 2-position of the indole ring of the compound (VII) thus obtained, a carbon functional group: Z-W-, Z-V-W- or Z-V- can be introduced in
15 accordance with the method disclosed by A. R. Kartitzky, "Tetrahedron Letters" vol. 26(48), P5935 (1985).

A compound of the formula (VIII) means an electrophilic reagent which can be reacted with an indole ring metalated in step b. Examples of a substrate usable
20 in such a reaction are illustrated below. For example, in the case of synthesizing a compound of the formula (VII) wherein W is $-\text{CH}_2-$ ($\text{R}^d=\text{H}$, $\text{R}^e=\text{H}$, $m=1$), a compound of the formula Z-A (A is $-\text{CH}_2-\text{B}$ (B is a leaving group in this reaction, such as a chlorine atom, a bromine atom,
25 an iodine atom, methanesulfonyl, benzenesulfonyl and p-toluenesulfonyl)) can be employed. When synthesizing a compound of the formula (VII) wherein W is $-\text{C}(=\text{O})-$ (R^d

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and R^e together form an oxo group and $m=1$), a compound of the formula Z-A (A is $-C(=O)-B$ (B is a leaving group in this reaction, such as OH, OLi, ONa, OK, a chlorine atom, a bromine atom, an iodine atom and methoxymethylamino, preferably OK, a chlorine atom, a bromine atom and methoxymethylamino)) can be employed. In the case of synthesizing a compound of the formula (VII) wherein W is $-C(OH)H-$ ($R^d=H$, $R^e=OH$, $m=1$), a compound of the formula Z-A (A is $-CHO$) can be employed. In the case of synthesizing a compound of the formula (VII) wherein W is $-C(OH)R^d-$ ($R^d=Me$ or Ph , $R^e=OH$, $m=1$), a compound of the formula Z-A (A is $-C(=O)-R^d$ ($R^d=Me$ or Ph)) can be employed. In the case of synthesizing a compound of the formula (VII) wherein V is $-S-$, a compound of the formula Z-A (A is $-S-S-Z$) can be employed.

When synthesizing a compound of the formula (VII) wherein V is $-SO_2-$, a compound of the formula Z-W-A or Z-A (A is SO_2-B (B is an eliminated group in this reaction, such as a halogen atom, preferably a chlorine atom)) can be employed. When synthesizing a compound of the formula (VII) wherein W-V is $CO-NH$, a compound of the formula Z-A (A is $-N=C=O$) can be employed.

A compound of the formula (VIII) may be a commercially available reagent or can be synthesized by a well known method.

In this case, lithium tetrahydrofuran, sodium hydroxide, potassium hydroxide, lithium, sodium,

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potassium, zinc, magnesium or copper, preferably s-butyl lithium or t-butyl lithium is used in an inert gas atmosphere such as nitrogen or argon. For example, in the case of using t-butyl lithium, the reaction is

5 conducted at a temperature of from -100°C to 100°C , preferably at -78°C , for 1 to 2 hours, and the reaction with a compound of the formula (VIII) is then conducted at -78°C . Thereafter, the reaction temperature is returned to room temperature, and a saturated ammonium

10 chloride aqueous solution is added thereto, and the reaction mixture is heated at 80°C - 120°C to obtain a compound of the formula (VII) or to isolate a carboxylic acid compound (VII) $\text{R}^{\text{n}}=\text{COOH}$ by recrystallization, which is then heated at 80°C - 200°C to conduct decarboxylation.

15 (Deprotection of hydroxymethyl group)

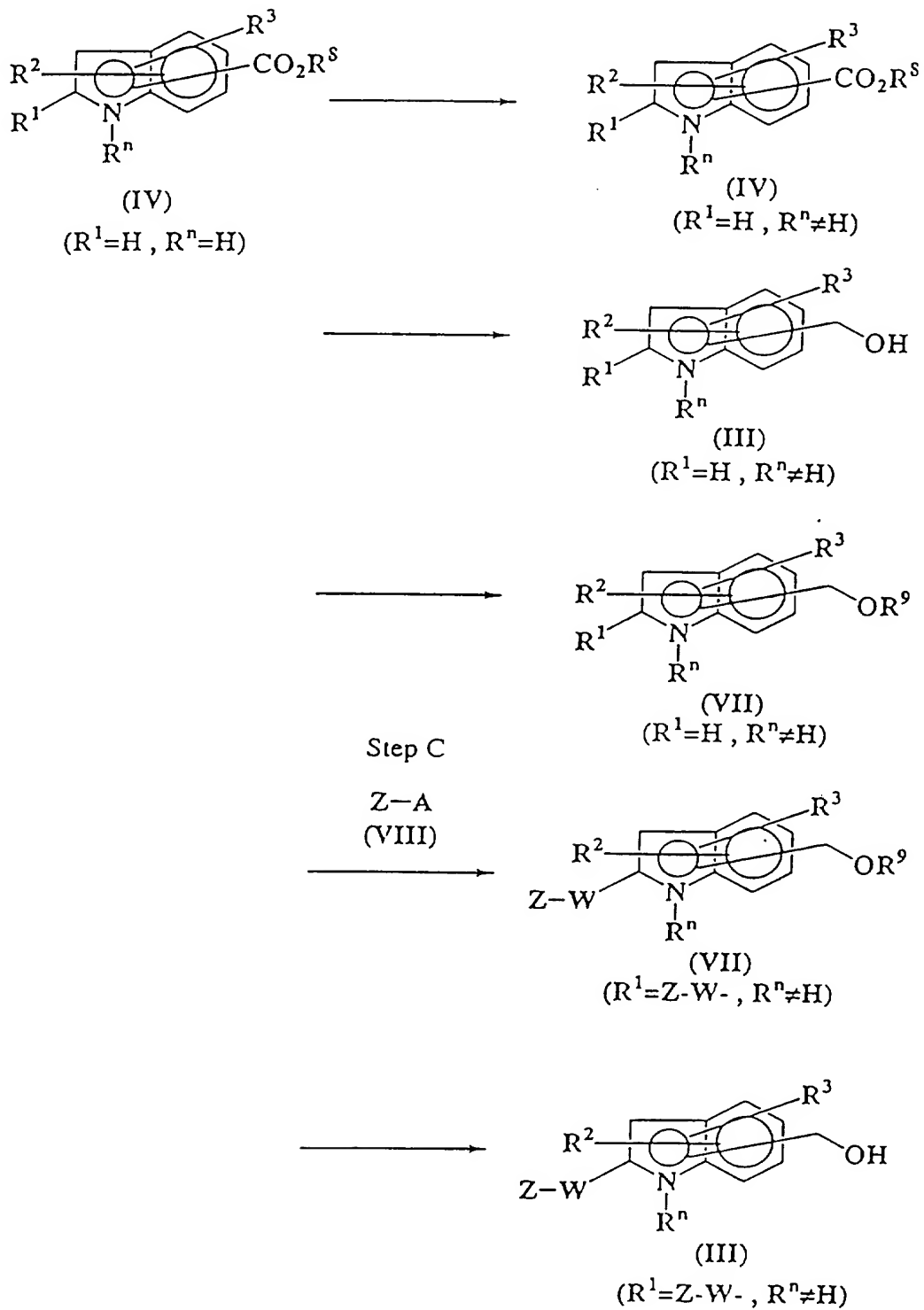
Deprotection of a primary hydroxymethyl group is conducted by means of a well known method. For example, deprotection of these alcohols is conducted in accordance with the method disclosed by T.W. Greene, P.G.M. Wuts

20 "Protective Groups in Organic Synthesis" (1991) to obtain a compound (III) wherein R^1 is introduced at the 2-position. When R^9 is t-butyldimethylsilyl, this reaction is conducted by using tetra-n-butylammonium fluoride in THF: Tetrahydrofuran at 0°C - 30°C in accordance with the

25 method disclosed in J. Amer. Chem. Soc., vol. 94, P6190(1972).

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Synthesis Route 3 Introduction of substituent R^1 at the 2-position of indole



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(wherein R^1 , R^2 , R^3 , R^8 , R^9 , R^n , W and Z are as defined above).

Among alkoxycarbonyl indoles of the formula (IV), a compound having an indole ring having hydrogen at the 1-
5 position and the 2-position can be converted to the corresponding hydroxymethyl indole (compound (III)) by introducing a carbon functional group: R^1 (Z-W-) by means of the following method.

The alkoxycarbonyl indole of the formula (IV) used
10 may be a commercially available reagent or may be obtained by esterifying indole carboxylic acid as a starting material by a well known method.

(Displacement of R^n substituent)

In this synthesis route, firstly a substituent: R^n
15 ($\neq H$) is introduced at the 1-position of an indole ring of alkoxycarbonyl indole (IV). Examples of R^n include a C_1 - C_7 alkyl group, a C_1 - C_4 alkoxymethyl group, a C_1 - C_4 alkylaminomethyl group, a carboxyl group, a C_1 - C_4 alkoxycarbonyl group, a C_1 - C_4 alkylaminocarbonyl group, a
20 C_1 - C_7 alkoxy group, a C_1 - C_7 alkoxyalkylmethoxy group, an alkylsulfonyl group and an aryl sulfonyl group, preferably methyl, methoxymethyl, dimethylaminomethyl, carboxyl, t-butyloxycarbonyl, methylcarbamoyl, methoxy, methoxymethoxy, mesyl, benzene sulfonyl, p-
25 toluenesulfonyl, p-methoxybenzenesulfonyl, p-fluorobenzenesulfonyl and p-chlorobenzenesulfonyl, more preferably benzene sulfonyl. When R^n is $PhSO_2$ -, this

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reaction is conducted by using benzenesulfonyl chloride, sodium hydride and n-butyl lithium in dimethylformamide at 0°C- 100°C in accordance with the method disclosed by R.J. Sundberg, "J. Org. Chem." vol. 38(19), P3324 (1973).

5 (Reduction of alkoxycarbonyl group)

The alkoxycarbonyl group of the compound (IV) thus obtained is reduced by using an appropriate reducing agent such as DIBAL: diisobutylaluminium hydride and LAH: lithium aluminum hydride by means of a well known method
10 to obtain the corresponding hydroxymethyl indole (compound (III)). This reaction is conducted, for example, in THF at 0°C-50°C.

(Protection of hydroxymethyl group)

The primary hydroxymethyl group of the hydroxymethyl
15 indole (compound (III)) is protected by means of a well known method to obtain a compound (VII). A protective group: R⁹ should be preferably stable under basic conditions in the following step, and the same protective group as used in Synthesis Route 1 can be used. For
20 example, when a t-butyldimethylsilyl group is used, a protective group can be introduced in the same manner as in Synthesis Route 1.

(Step c)

In the compound (VII) thus obtained, a carbon
25 functional group R¹ can be introduced at the 2-position of the indole ring in accordance with the method disclosed by R.J. Sundberg, "J. Org. Chem.", vol. 38

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(19), P3324 (1973).

In this reaction, a compound of the formula (VII) is reacted with a base to anionize the 2-position under an inert gas atmosphere such as nitrogen or argon in an aprotic organic solvent such as tetrahydrofuran, ether, isopropyl ether, n-pentane, i-pentane, cyclopentene, n-hexane, cyclohexane, HMPA: hexamethylphosphoric triamide, HMPT: hexamethylphosphorous triamide, N,N,N',N'-tetramethylethylenediamine, dioxane, dimethylsulfoxide or dimethylformamide. Examples of the base used include n-butyl lithium, s-butyl lithium, t-butyl lithium, phenyl lithium, methyl lithium, LDA: lithium diisopropyl amide, potassium bis(trimethylsilyl)amide, calcium hydride, sodium hydride, potassium hydride, potassium carbonate, lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium, sodium, potassium, zinc, magnesium or copper, preferably n-butyl lithium, s-butyl lithium, t-butyl lithium or LDA. For example, when t-butyl lithium is used, the reaction is conducted at a temperature of from -100°C to 100°C, preferably from -78°C to 0°C, for 10 to 120 minutes, and then the reaction with a compound of the formula (VIII) is conducted to introduce a carbon functional group at the 2-position of the indole ring. A compound of the formula (VIII) may be a commercially available reagent or may be synthesized in the same manner as above.

(Deprotection of hydroxymethyl group)

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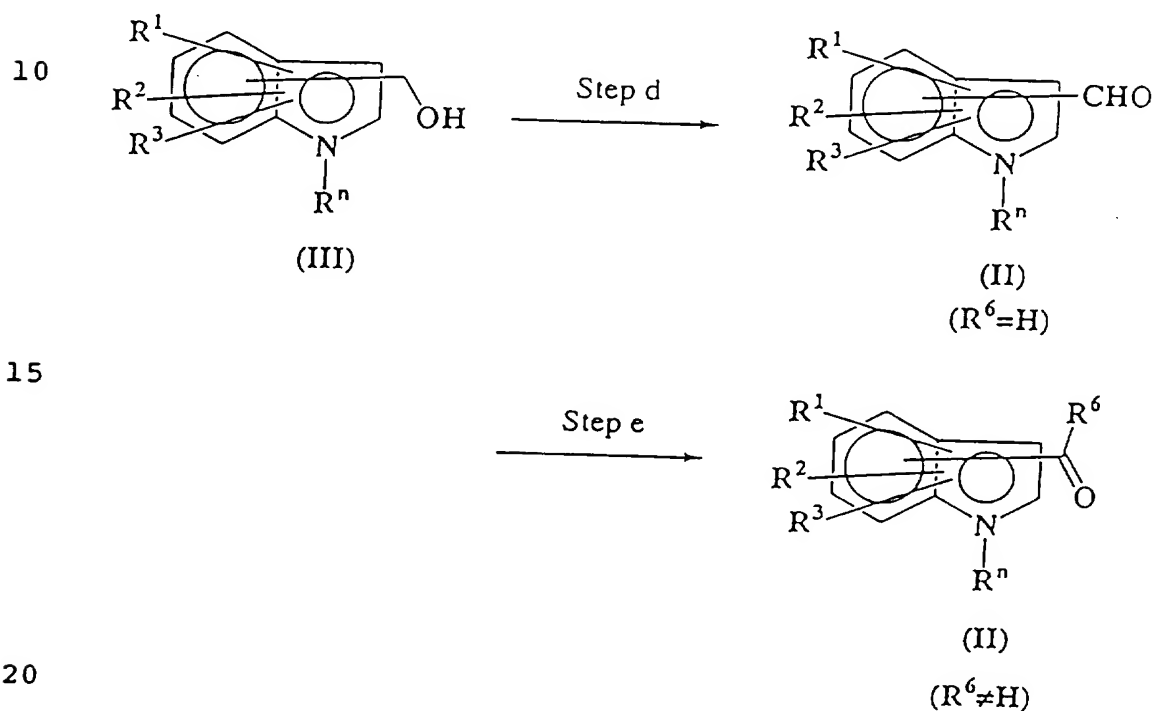
The deprotection of a primary hydroxymethyl group is conducted by means of a well known method to obtain a compound (III) having R^1 introduced at the 2-position.

When R^9 is t-butyldimethylsilyl, this reaction is

5 conducted under the same conditions as in Synthesis Route 1.

Method for preparing intermediate (II)

Synthesis Route 1



(wherein R^1 , R^2 , R^3 , R^6 and R^n are as defined above).

A carbonyl indole of the formula (II) is a well known compound or can be obtained by oxidizing a hydroxymethyl indole of the formula (III). This step is conducted by
25 using an appropriate oxidizing agent (such as manganese dioxide, PCC: pyridiniumchlorochromate, PDC:

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pyridiniumdichromate, DDQ: dichlorodicyanobenzoquinone, chloranil, Swern oxidizing agent: oxalyl chloride-dimethylsulfoxide-tertiary amine or sulfur trioxide-pyridine complex).

- 5 An example of using pyridine chromic acid complex as an oxidizing agent is disclosed in Japanese Examined Patent Publication No. 34986/1974.

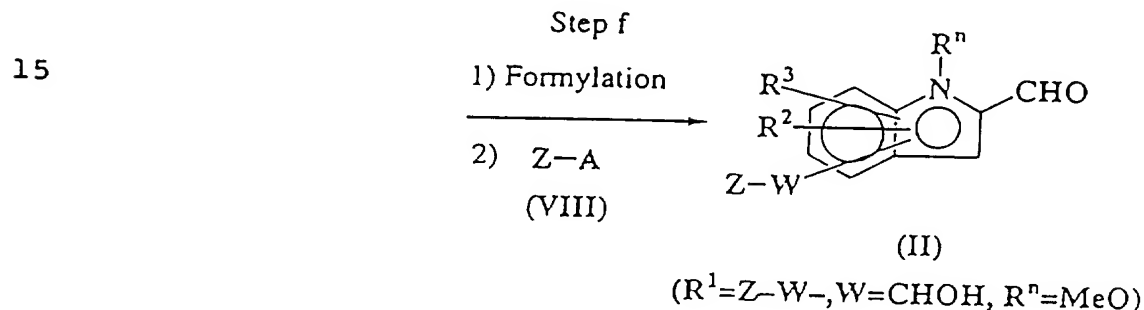
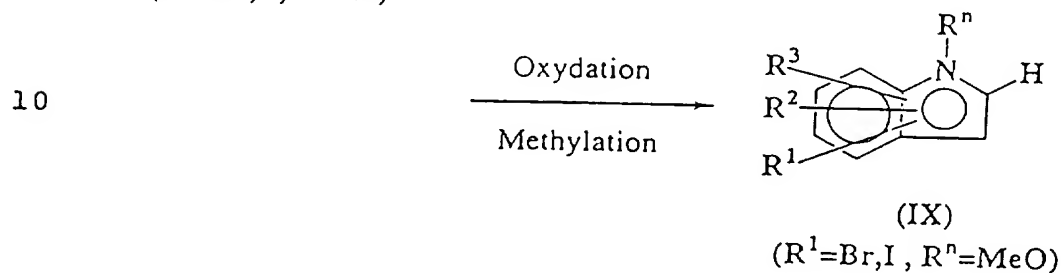
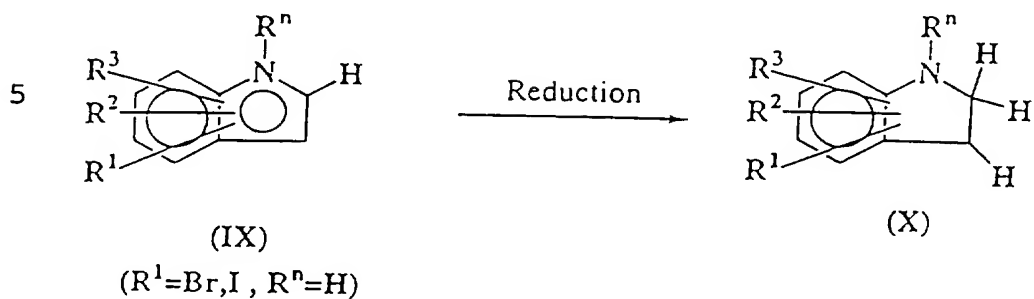
 A formylindole of the formula (II) ($R^6=H$) obtained by the above method can be converted to a carbonylindole of
10 the formula (II) ($R^6 \neq H$) by alkylating the formyl group with an appropriate alkylating agent.

 This step can be conducted by the method using diazomethane as disclosed in "Tetrahedron Letters" P955 (1963) and "Chem. Ber." vol. 40, P479 (1907), the method
15 using alkyl halide as disclosed in "Synth. Commun." vol. 14(8), P743 (1984) or the method using alkyl lithium as disclosed in "J. Org. Chem." vol. 30, P226 (1965).

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Synthesis Route 2

Introduction of substituent R^1 and formylation at the 2-position of indole



20 (wherein R^1, R^2, R^3, R^n, W and Z are as defined above).

Among formylindoles of the formula (II) ($R^6 = \text{H}$), a compound having a formyl group at the 2-position of an indole ring and having a carbon functional group R^1 at the 4-, 5-, 6- or 7-position can be synthesized by the following method.

25 A carbon functional group: R^1 can be introduced in the indole nucleus by protecting a nitrogen atom at the

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1-position of haloindole of the formula (IX) with a lower alkoxy group, particularly a methoxy group, conducting formylation at the 2-position, conducting metalation of the haloindole in the presence of a strong base and then
5 reacting with an aldehyde compound of the formula (XI).
(Reduction of indole ring)

A haloindole (IX) used as a starting material has a hydrogen atom at the 1-position and a halogen atom at the 4-, 5-, 6- or 7-position. The halogen atom is preferably
10 bromine or iodine, more preferably bromine, and the haloindole (IX) used is a commercially available reagent or can be synthesized by a well known method. The haloindole (IX) can be converted into the corresponding indoline (compound (X)) by reducing at the 2- and 3-
15 positions of the indole ring, for example, by the method disclosed in "J. Amer. Chem. Soc. " vol. 96, P7812 (1974).

(Synthesis of methoxyindole by oxidation and methylation of indoline)

20 The indoline (compound (X)) can be converted into the corresponding 1-methoxyhaloindole (compound (IX)) by conducting oxidation and methylation at the 2-, 3- and 1-positions in accordance with the method disclosed in Japanese Unexamined Patent Publication No. 31257/1991 (M. Somei). This reaction is conducted by oxidizing with a
25 30% hydrogen peroxide aqueous solution in a methanol/water mixture solvent in the presence of

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disodium tungstate dihydrate as a catalyst at 0°C and then methylating with diazomethane or dimethylsulfuric acid: potassium carbonate at room temperature.

(Step f)

5 1-methoxyhaloindole (compound (IX)) can be converted to the aimed formylindole (compound (II)) by conducting formylation at the 2-position and then reacting with compound (VIII) in accordance with the method disclosed in "Heterocycles" by M. Somei, vol. 132, P221 (1991).

10 The 2-position of 1-methoxyhaloindole is anionized by reacting with a base under an inert gas atmosphere such as nitrogen or argon in an aprotic organic solvent such as tetrahydrofuran, ether, isopropyl ether, n-pentane, i-pentane, cyclopentane, n-hexane, cyclohexane, HMPA:

15 hexamethylphosphoric triamide, HMPT:

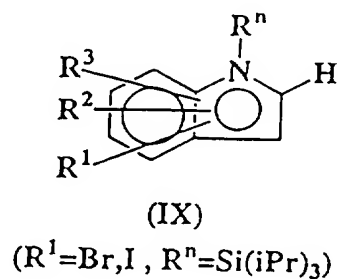
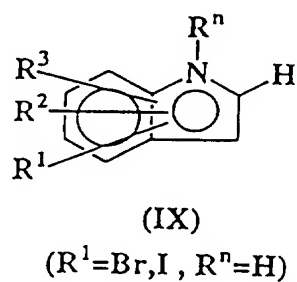
hexamethylphosphorous triamide, N,N,N',N'-

tetramethylethylene diamine, dioxane, dimethylsulfoxide or dimethylformamide. Examples of such a base include n-butyl lithium, s-butyl lithium, t-butyl lithium, phenyl

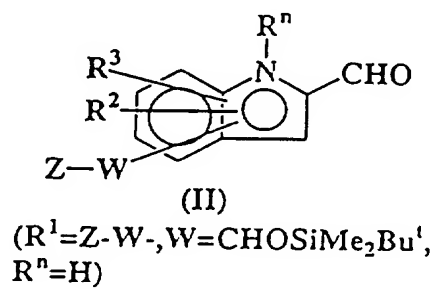
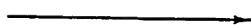
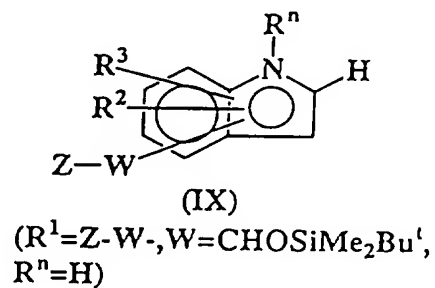
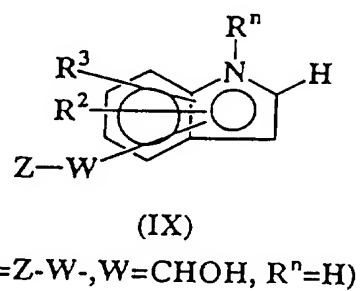
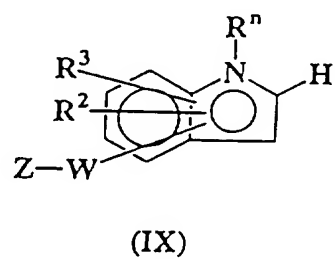
20 lithium, methyl lithium, LDA: lithium diisopropyl amide, potassium bis(trimethylsilyl)amide, calcium hydride, sodium hydride, potassium hydride, potassium carbonate, lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium, sodium, potassium, zinc, magnesium and copper,
25 preferably phenyl lithium, n-butyl lithium and LDA. For example, when phenyl lithium is used, the reaction is conducted for 10-120 minutes by lithium-modifying the 2-

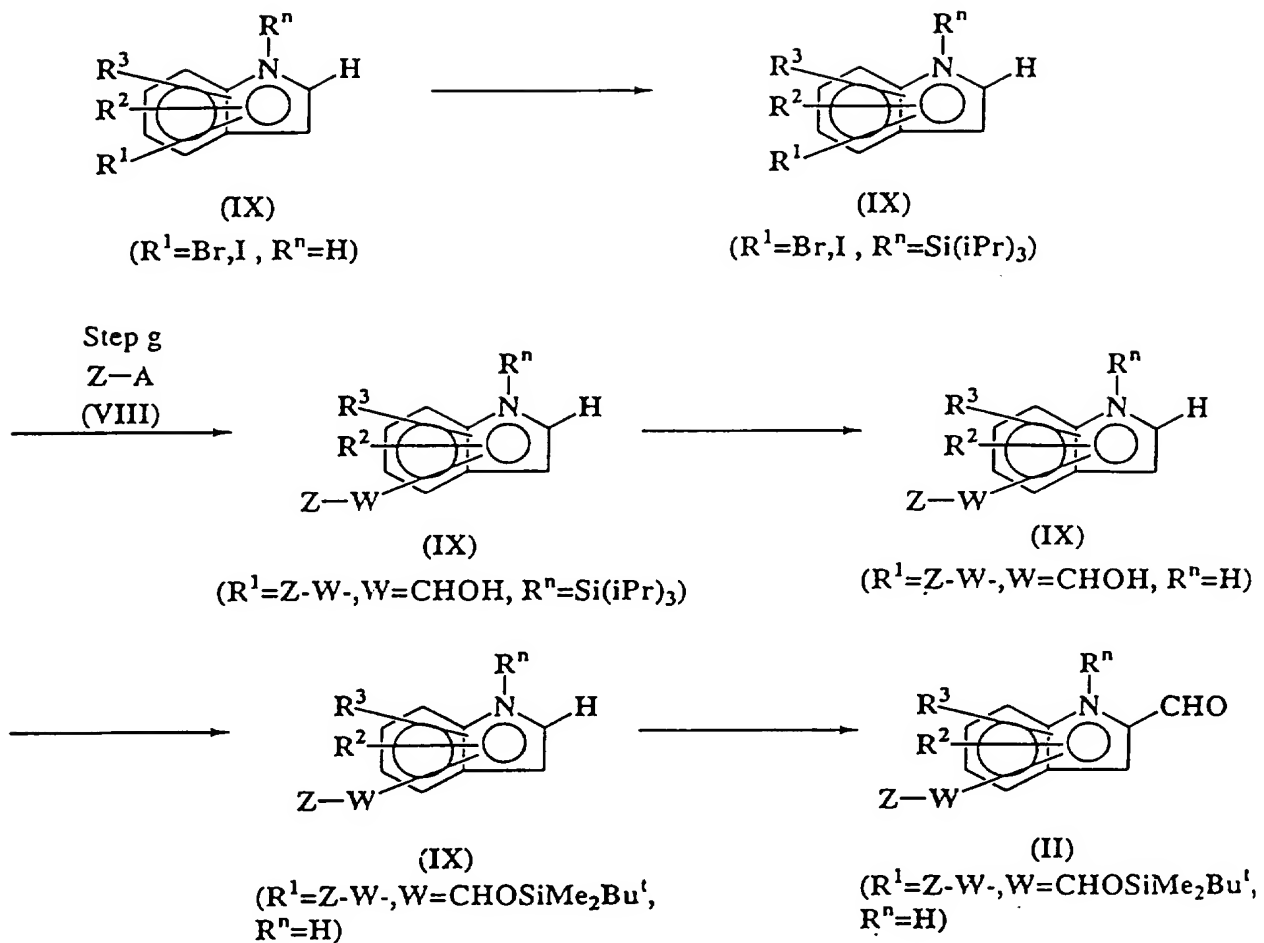
- 116 -

position in tetrahydrofuran at a temperature of from -100°C to 100°C, preferably from -78°C to 0°C, and reaction with N,N'-dimethylformamide, N,N'-methoxymethylformamide is then conducted for 5 to 120 minutes. Thereafter, the 5-position is anionized by further reacting with a base at a temperature of from -100°C to 100°C, preferably from -78°C to 0°C. Examples of the base used include n-butyl lithium, s-butyl lithium, t-butyl lithium, phenyl lithium, methyl lithium, LDA: lithium diisopropylamide, potassium bis(trimethylsilyl)amide, calcium hydride, sodium hydride, potassium hydride, potassium carbonate, lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium, sodium, potassium, zinc, magnesium and copper, preferably s-butyl lithium and t-butyl lithium. For example, when t-butyl lithium is used, after reacting for 10 to 120 minutes, reaction with the compound of the formula (VIII) is conducted to obtain the aimed formyl indole (compound (II)).

Synthesis Route 3

Step g

Z-A
(VIII)



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(wherein R^1 , R^2 , R^3 , R^n , W and Z are as defined above).

Among formylindoles of the formula (II) ($R^6=H$), an indole having a formyl group at the 2-position of the indole ring and having a carbon functional group: R^1 at the 4-, 5-, 6- or 7-position can be synthesized by the following method.

After protecting a nitrogen atom at the 1-position of a haloindole of the formula (IX) with a substituted silyl group, the haloindole is subjected to metalation in the presence of a strong base and was reacted with an aldehyde compound of the formula (VIII) to introduce a carbon functional group into the indole ring. Thereafter, the silyl group at the 1-position is deprotected and the 2-position is formylated to obtain a formylindole (intermediate (II)).

The haloindole (IX) ($R^1=Br$, I , $R^n=H$) used as a starting material has a hydrogen atom at the 1-position and a halogen atom at the 4-, 5-, 6- or 7-position. The halogen atom is preferably bromine or iodine, more preferably bromine and the haloindole used may be a commercially available reagent or may be prepared by a well known method.

(Introduction of substituent R^n)

An appropriate substituent is introduced into the haloindole (IX) by a well known method. Examples of the substituent include a substituted silyl group, a C_1 - C_7 acyl group, a C_1 - C_4 alkoxycarbonyl group and a C_1 - C_4

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alkylaminocarbonyl group, preferably pivaloyl, t-butyl
oxycarbonyl, t-butyl carbamoyl, triisopropylsilyl, t-
butyldimethylsilyl and t-butyldiphenylsilyl, more
preferably triisopropylsilyl, t-butyldimethylsilyl and t-
5 butyldiphenylsilyl.

(Step g)

The 5-position of the compound of the formula (IX)
($R^1 = \text{Br}$, I, $R^n = \text{H}$) is anionized by reacting with a base
under an inert gas atmosphere such as nitrogen or argon
10 in an aprotic organic solvent such as tetrahydrofuran,
ether, isopropyl ether, n-pentane, i-pentane,
cyclopentane, n-hexane, cyclohexane, HMPA:
hexamethylphosphoric triamide, HMPT:
hexamethylphosphorous triamide, N,N,N',N'-
15 tetramethylethylene diamine, dioxane, dimethylsulfoxide
or dimethylformamide, preferably tetrahydrofuran or
ether. Examples of the based used include n-butyl
lithium, s-butyl lithium, t-butyl lithium, phenyl
lithium, methyl lithium, LDA: lithium diisopropyl amide,
20 potassium bis(trimethylsilyl)amide, calcium hydride,
sodium hydride, potassium hydride, potassium carbonate,
lithium hydroxide, sodium hydroxide, potassium hydroxide,
lithium, sodium, potassium, zinc, magnesium and copper,
preferably n-butyl lithium, s-butyl lithium, t-butyl
25 lithium and methyl lithium. For example, when t-butyl
lithium is used, the reaction is conducted in ether at a
temperature of from -100°C to 100°C , preferably -78°C to

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0°C, for 10 to 120 minutes, and the reaction product is further reacted with a compound of the formula (VIII) to obtain a compound (IX) ($R^1=Z-W-$, $W=CHOH$, $R^n=Si(iPr)_3$).
(Removal of R^n substituent)

5 A compound of the formula (IX) ($R^1=Z-W-$, $W=CHOH$, $R^n=Si(iPr)_3$) can be converted to a compound of the formula (IX) ($R^1=Z-W-$, $W=CHOH$, $R^n=H$) by reacting with tetra-n-butylammonium fluoride in tetrahydrofuran or ether at room temperature.

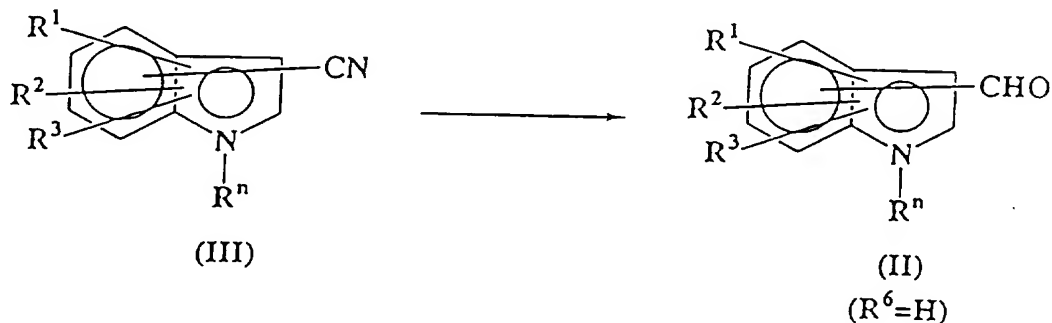
10 (Protection of hydroxy group)

A compound of the formula (IX) ($R^1=Z-W-$, $W=CHOH$, $R^n=H$) can be converted to a compound of the formula (IX) ($R^1=Z-W-$, $W=C(H)OSiMe_2t-Bu$, $R^n=H$) by reacting with tertiary butyldimethylsilyl chloride in the presence of
15 imidazole in dimethylformamide.

(Formylation at the 2-position of indole ring)

A compound of the formula (IX) ($R^1=Z-W-$, $W=C(H)OSiMe_2t-Bu$, $R^n=H$) can be converted into a formylated product (II) by the method disclosed in "J.
20 Am. Chem. Soc." of A. R. Katritzky, vol. 108, P 6808 (1986).

Synthesis Route 4



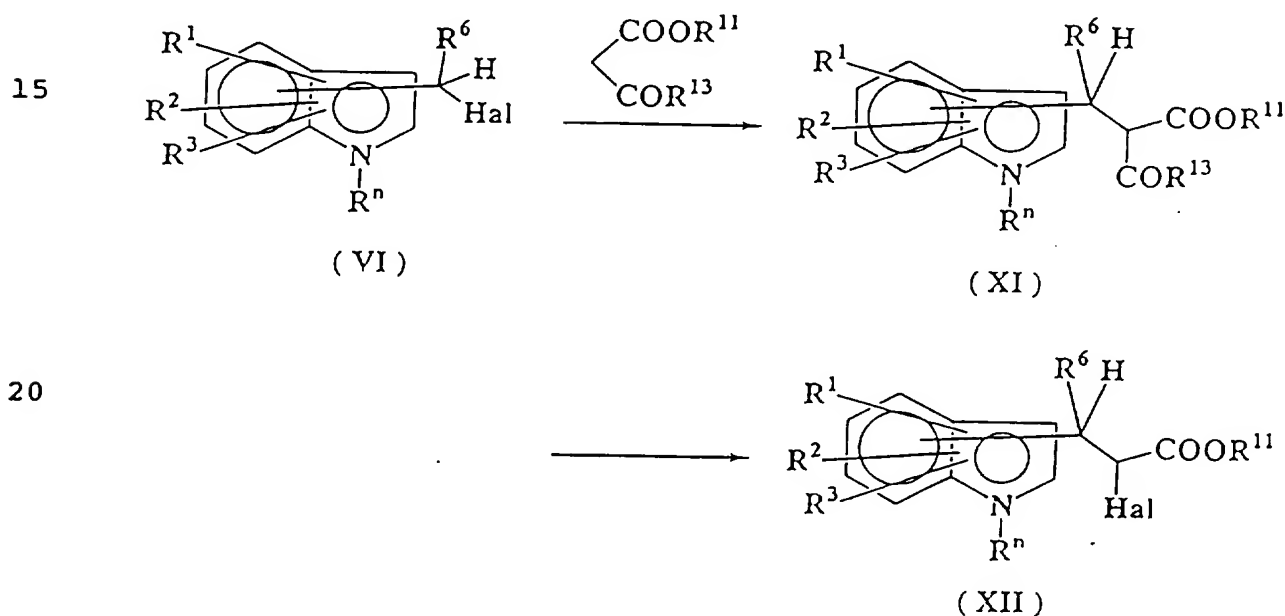
- 122 -

(wherein R^1 , R^2 , R^3 and R^n are as defined above).

The formylated product (II) can be obtained by reducing a cyano group of an indole of the formula (XIII). This step can be conducted by using an appropriate reducing agent (such as Raney nickel, nickel, sodium aluminum hydride, sodium triethoxyaluminum hydride, diisobutylaluminum hydride and tin chloride (II)).

An example of reducing an indole (XIII) by using Raney nickel is described in Japanese Unexamined Patent Publication No. 151172/1986.

Method for preparing intermediate (XII)



25 (wherein R^1 , R^2 , R^3 , R^6 , R^{11} , Z and Hal are as defined above, and R^{13} is OR^{11} (R^{11} is as defined above) or C_1 - C_3 alkyl such as methyl, ethyl, n-propyl and i-propyl).

- 123 -

A halocarboxylic acid ester of the formula (XII) can be obtained by reacting a halomethylindole of the formula (VI) with a malonic acid ester or a lower acylacetic acid ester by a well known method to obtain a compound of the formula (XI) and halogenating the compound of the formula (XI) thus obtained.

The halomethylindole of the formula (VI) can be synthesized by the method disclosed in "Org. Prep. Proced. Int." vol. 25, P249 (1993). Thus, the halomethylindole of the formula (VI) can be obtained by halogenating a hydroxymethylindole of the formula (III) with an appropriate halogenating agent (such as SOCl_2 , POCl_3 , PCl_5 , HCl , SnCl_4 , HBr , PBr_3 , Br_2 , POBr_3 , methanesulfonic acid chloride, p-toluenesulfonic acid chloride, N-bromosuccinimide-triphenylphosphine and N-chlorosuccinimide-triphenylphosphine).

Among compounds of the formula (XI), a compound wherein R^{13} is $\text{C}_1\text{-C}_3$ alkyl, can be obtained by reacting a halomethylindole of the formula (VI) with a lower acylacetic acid ester such as methyl acetoacetate or ethyl acetoacetate in the presence of an appropriate base (such as sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium amide, potassium amide, diisopropylamide, butyl lithium, metallic sodium, potassium carbonate, sodium hydride, potassium hydride and calcium hydride) in accordance with the method disclosed in "J. Amer. Chem. Soc." vol 64, P435 (1942).

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Among compounds of the formula (XII), a compound wherein R^{13} is OR^{11} , can be obtained by reacting a halomethylindole of the formula (VI) with a malonic acid ester such as diethyl malonate or di-*t*-butyl malonate in the presence of such a base as mentioned above, in accordance with the method disclosed in "J. Amer. Chem. Soc." vol 74, P831 (1952).

The step for preparing a compound of the formula (XII) is conducted by using an appropriate halogenating agent (such as bromine or *N*-chlorosuccinimide) in the presence of an appropriate base (such as potassium hydroxide, sodium methoxide or potassium carbonate) in accordance with the method disclosed in "J. Amer. Chem. Soc." vol 71, P3107 (1949) or "Tetrahedron Letters" vol. 28, P5505 (1987).

Also, a compound of the formula (XII) can be obtained by reacting a halomethylindole of the formula (VI) with a diazoacetic acid ester in the presence of a copper catalyst in accordance with the method disclosed in "Zur. Russ. Fiz-Chim." vol. 21, P851 (1951).

Among the above-mentioned compounds (II), (III), (VII) and (IX), the compound having a carbon functional group as R^1 is a novel compound and is useful as an intermediate for preparing the compound of the formula (I).

Examples of the compound of the present invention are illustrated as compounds of the formulas (I-1) and (I-2)

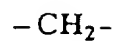
- 125 -

in Tables 1 to 10. Also, the above described salts derived by reacting basic nitrogen at the 3-position of the thiazolidine ring by means of a well known method are also the compounds of the present invention.

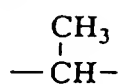
5 In the Tables, Me is a methyl group; Et is an ethyl group; Pr is a propyl group; Bu is a butyl group; Pen is a pentyl group; Hex is a hexyl group; Hep is a heptyl group; Ph is a phenyl group; n means "normal"; i means "iso"; s means "secondary"; t means "tertiary"; and c
10 means "cyclo". Also, Q1 to Q317 and J1 to J42 represent the following substituents.

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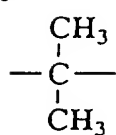
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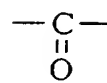
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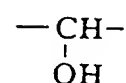
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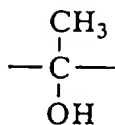
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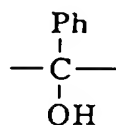
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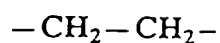
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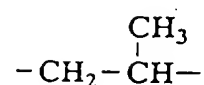
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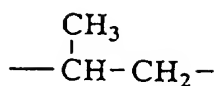
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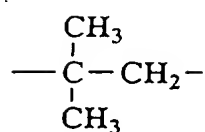
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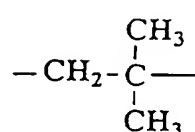
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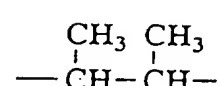
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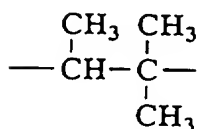
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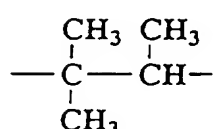
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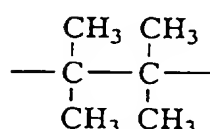
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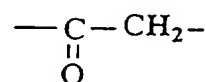
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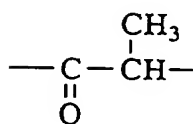
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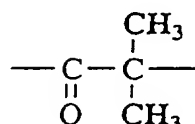
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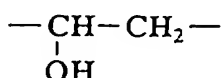
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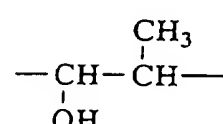
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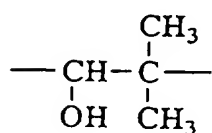
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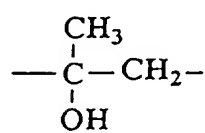
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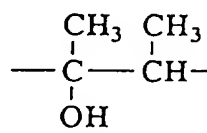
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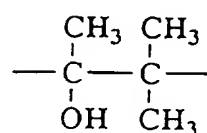
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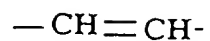


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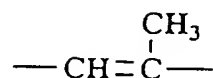
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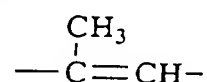
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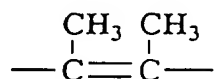
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J29



J30



J31



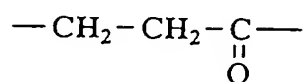
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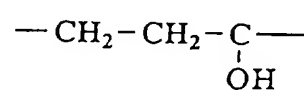
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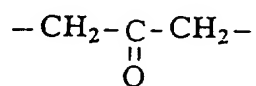
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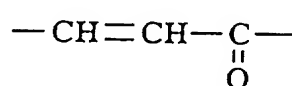
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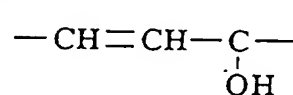
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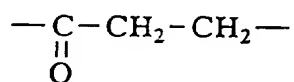
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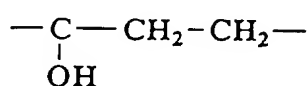
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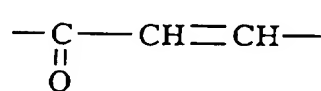
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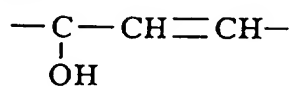
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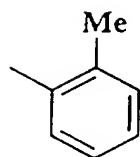
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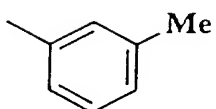
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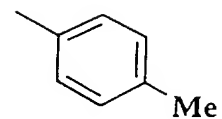
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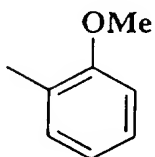
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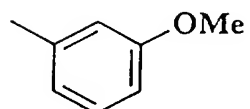
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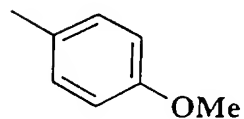
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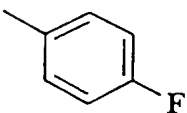
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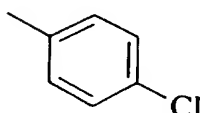
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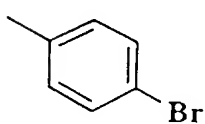
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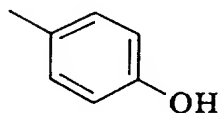
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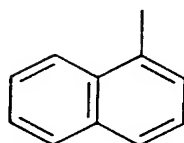
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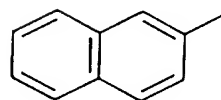
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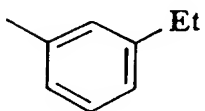
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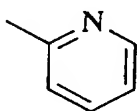
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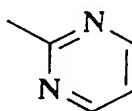
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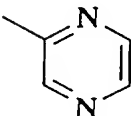
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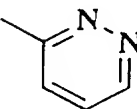
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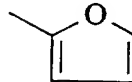
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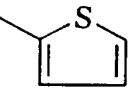
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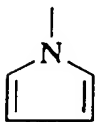
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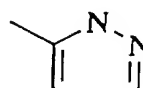
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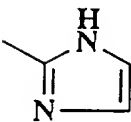
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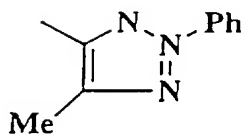
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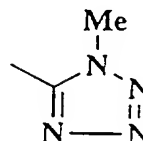
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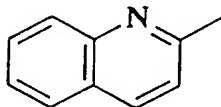
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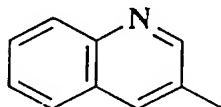
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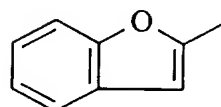
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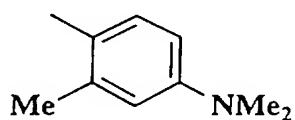
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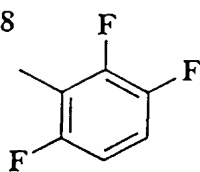
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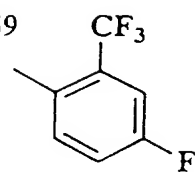
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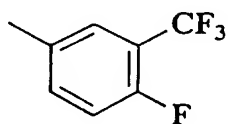
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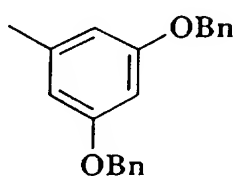
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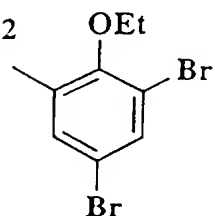
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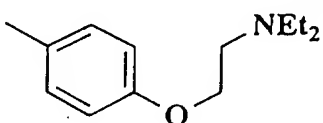
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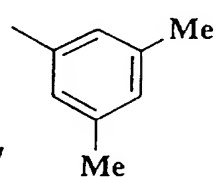
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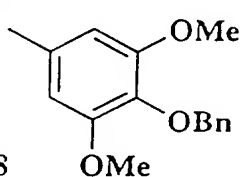
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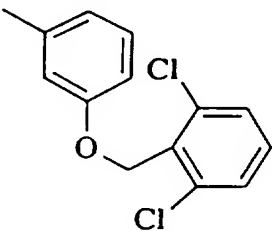
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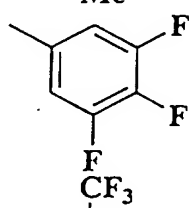
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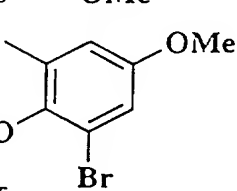
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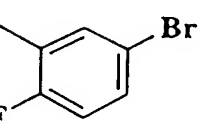
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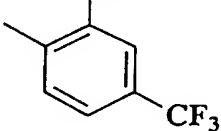
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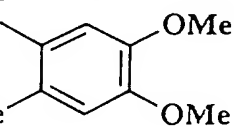
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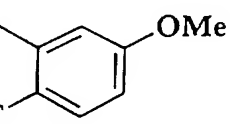
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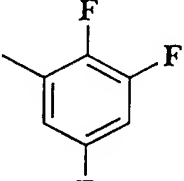
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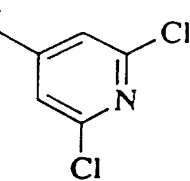
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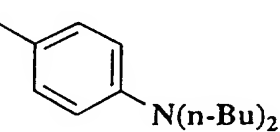
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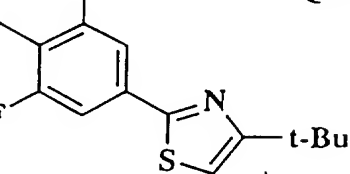
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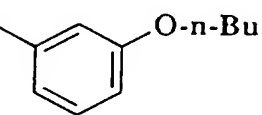
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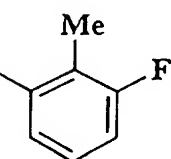
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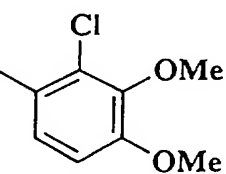
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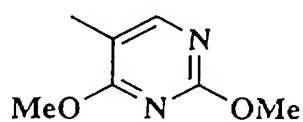
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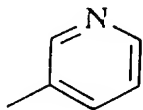
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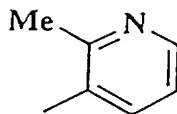
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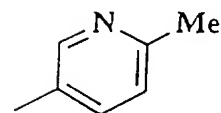
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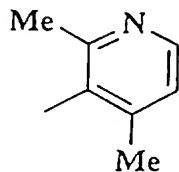
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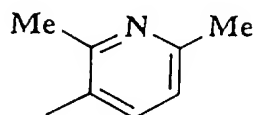
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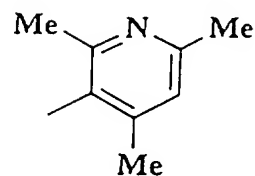
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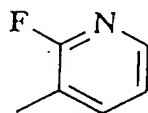
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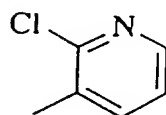
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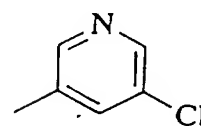
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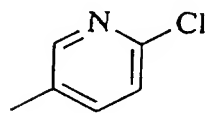
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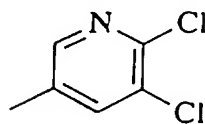
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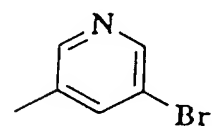
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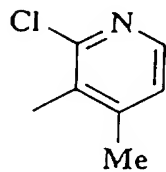
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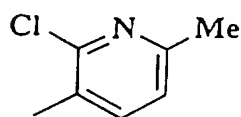
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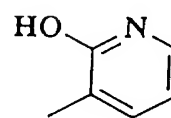
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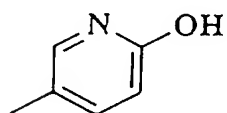
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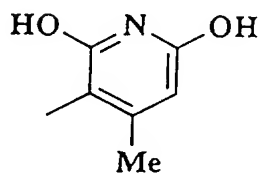
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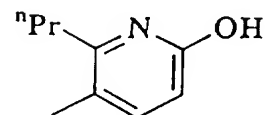
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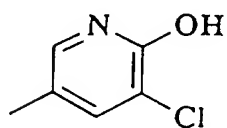
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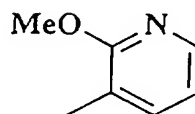
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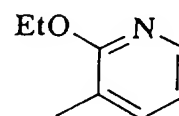
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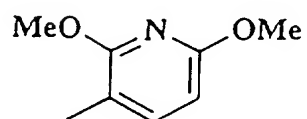
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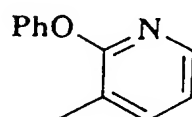
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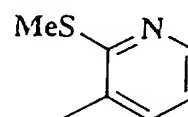
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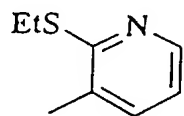


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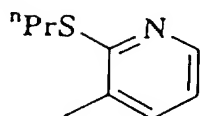


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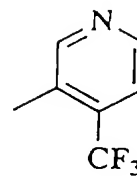
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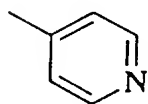
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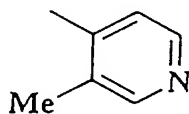
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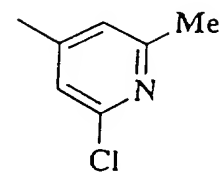
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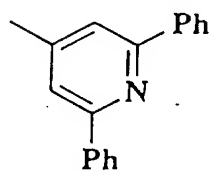
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Q78



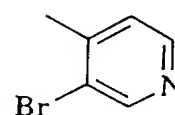
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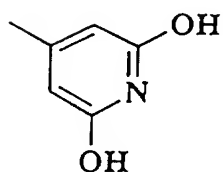
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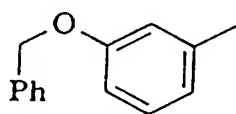
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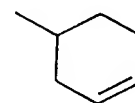
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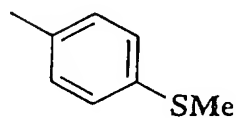
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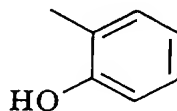
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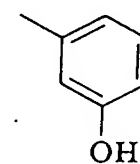
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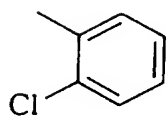
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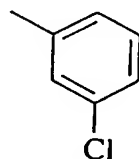
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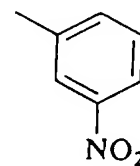
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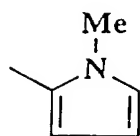
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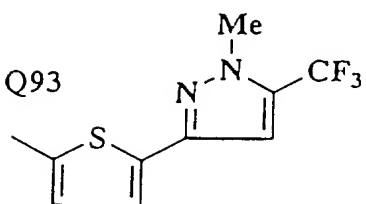
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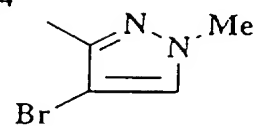
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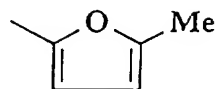
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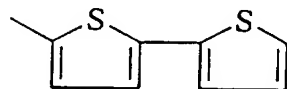
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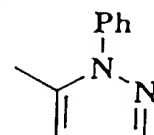
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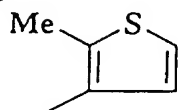
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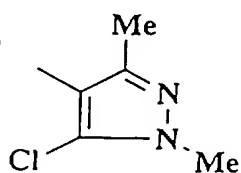
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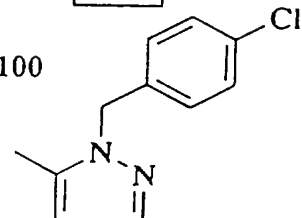
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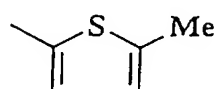
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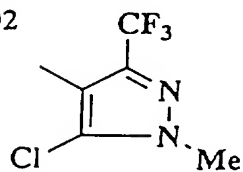
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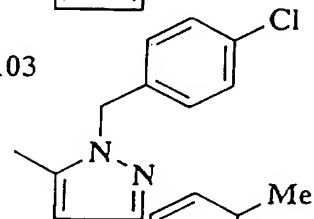
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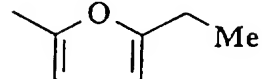
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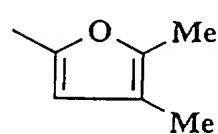
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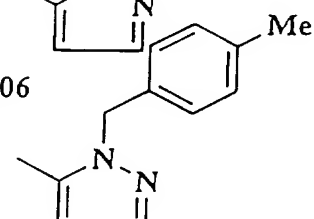
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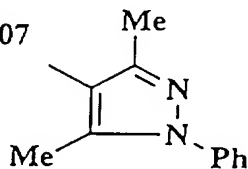
Q105



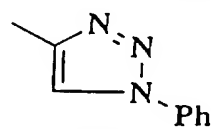
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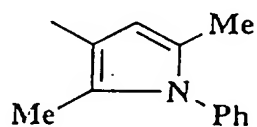
Q107



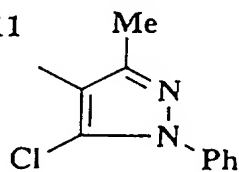
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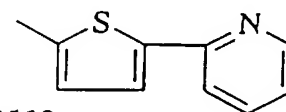
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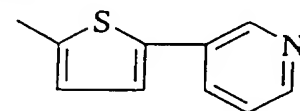
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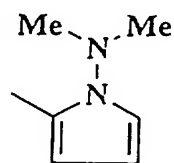
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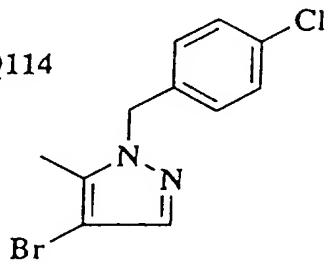
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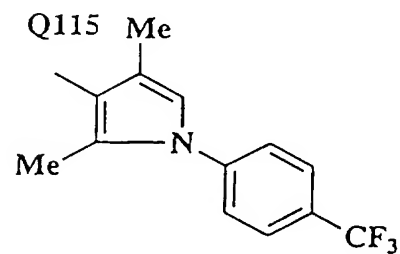
Q113



Q114

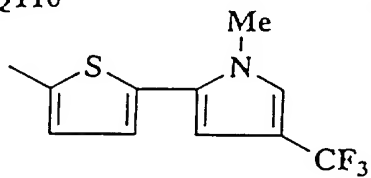


Q115

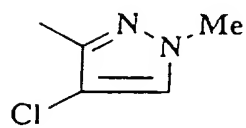


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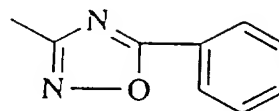
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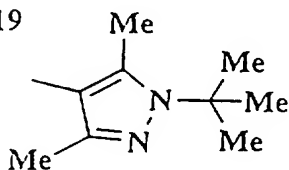
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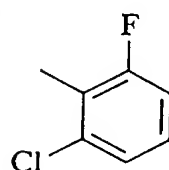
Q 118



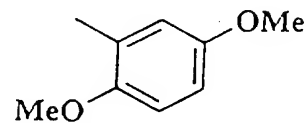
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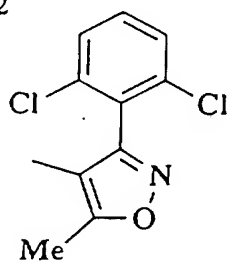
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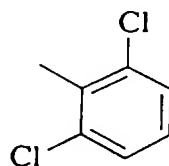
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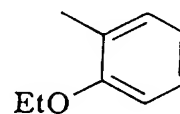
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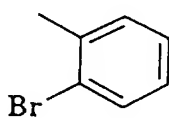
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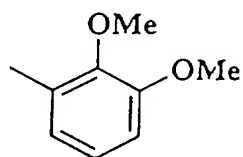
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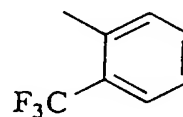
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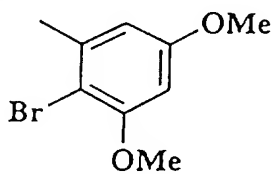
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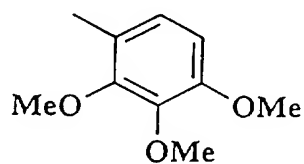
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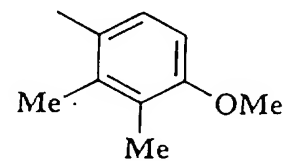
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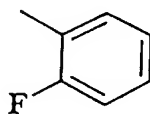
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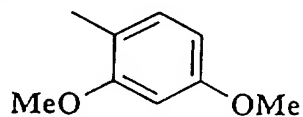
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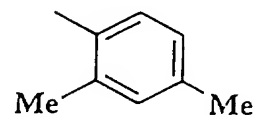
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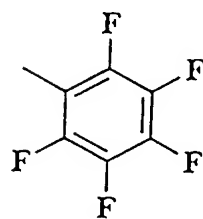
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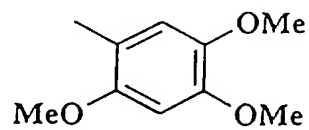
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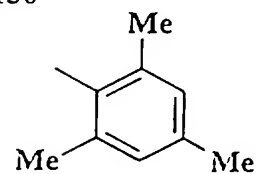
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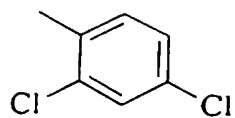
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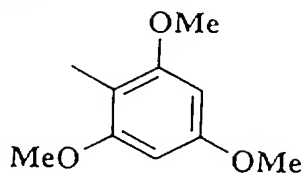
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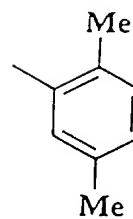
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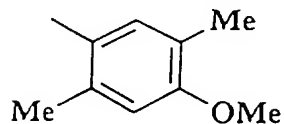
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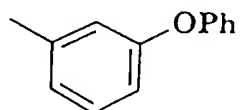
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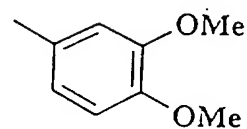
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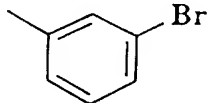
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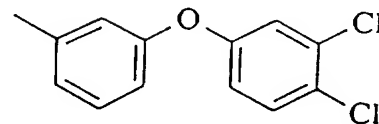
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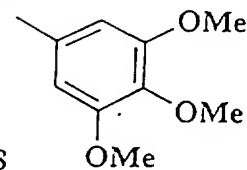
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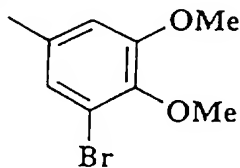
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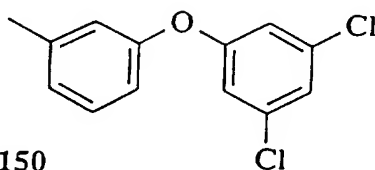
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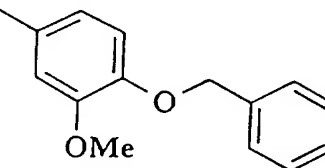
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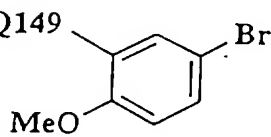
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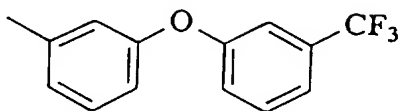
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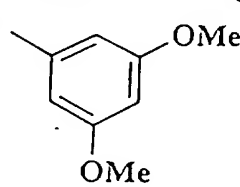
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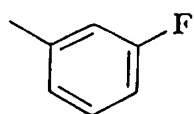
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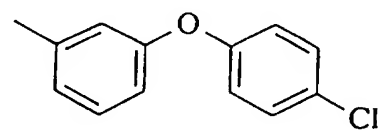
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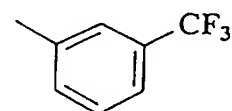
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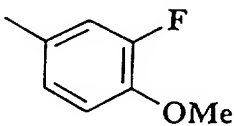
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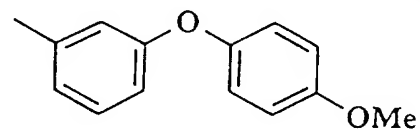
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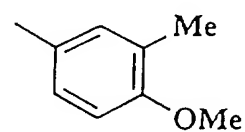
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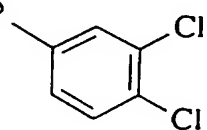
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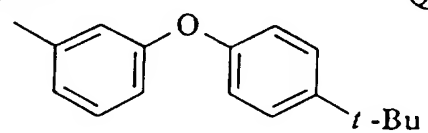
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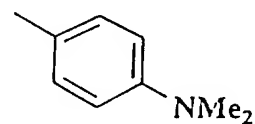
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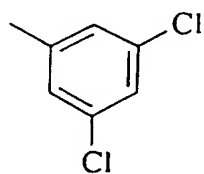
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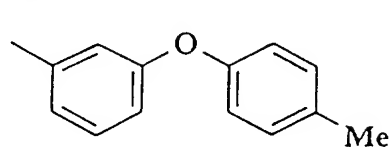
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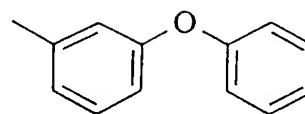
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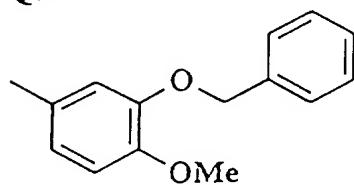
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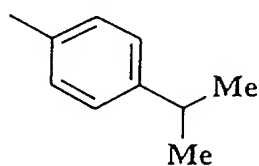
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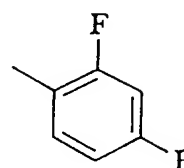
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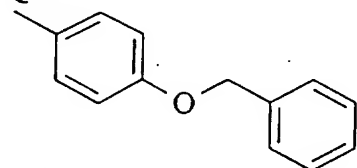
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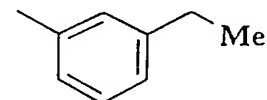
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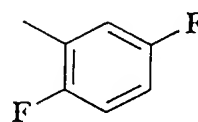
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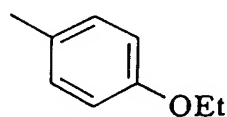
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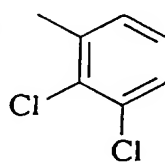
Q169



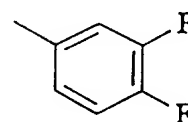
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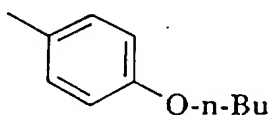
Q171



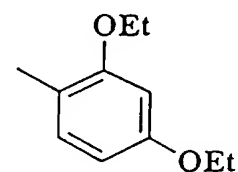
Q172



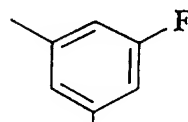
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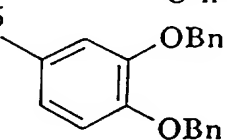
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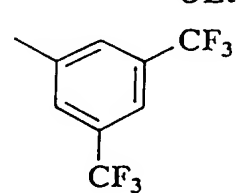
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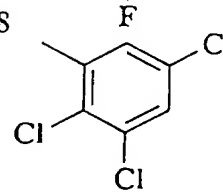
Q176



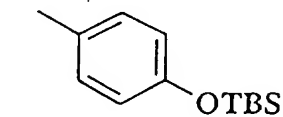
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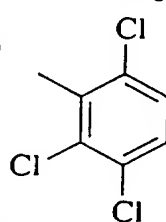
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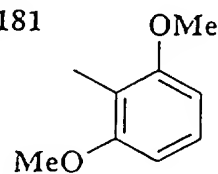
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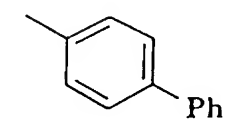
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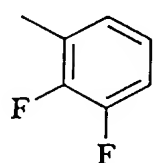
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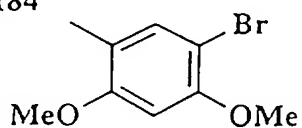
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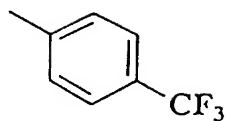
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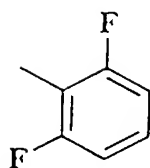
Q184



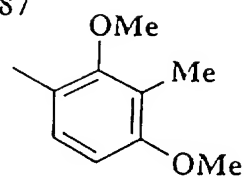
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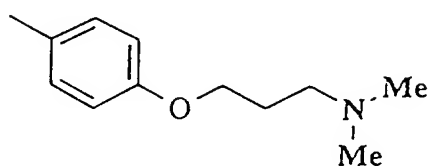
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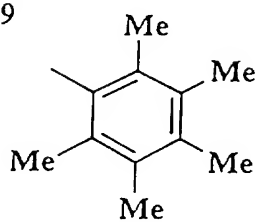
Q187



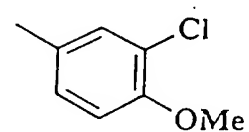
Q188



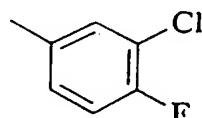
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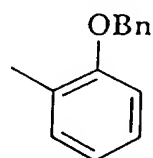
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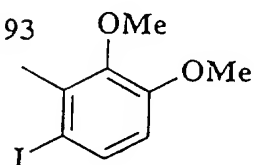
Q191



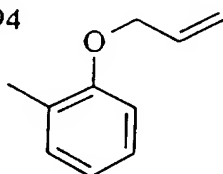
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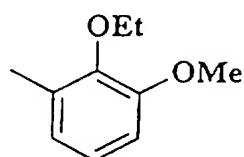
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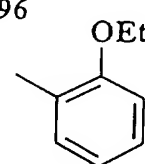
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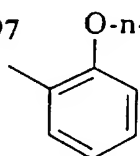
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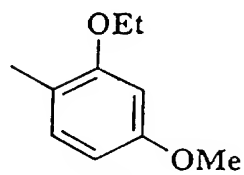
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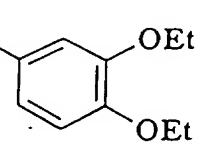
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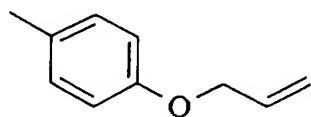
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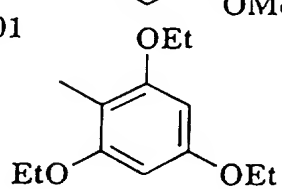
Q199



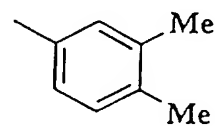
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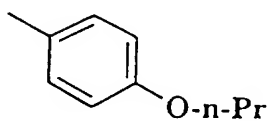
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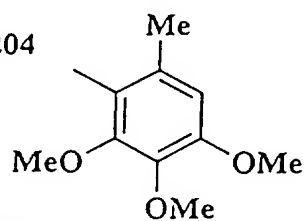
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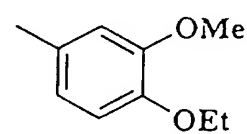
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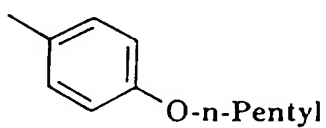
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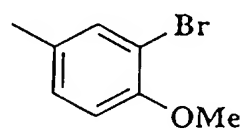
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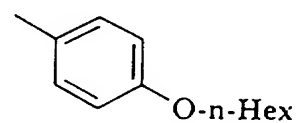
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Q207

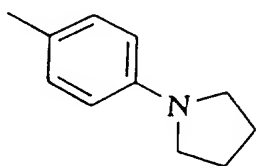


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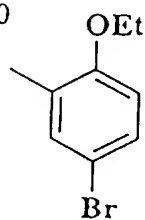


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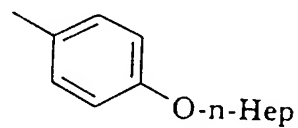
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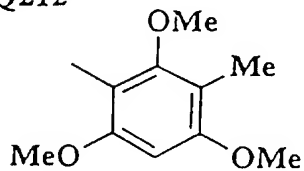
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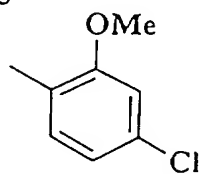
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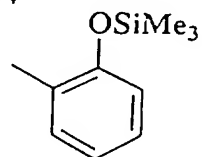
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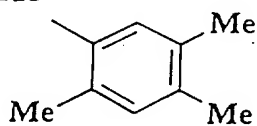
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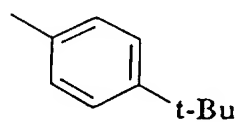
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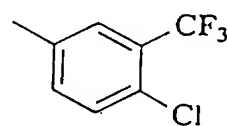
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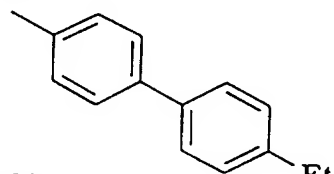
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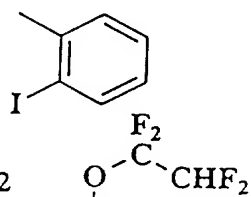
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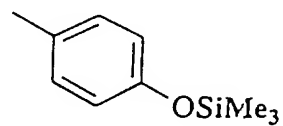
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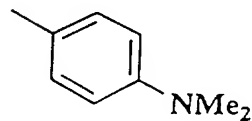
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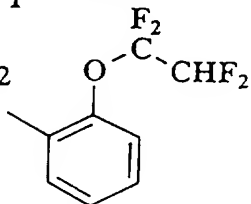
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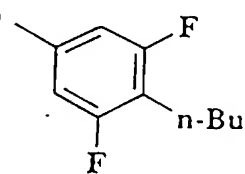
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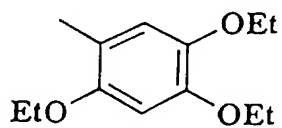
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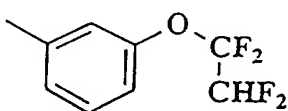
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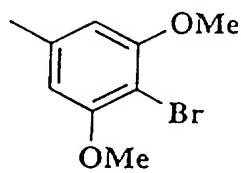
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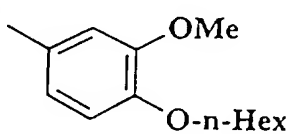
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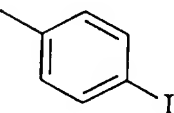
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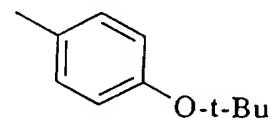
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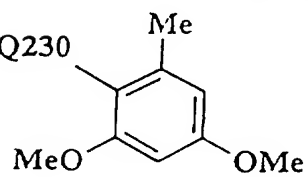
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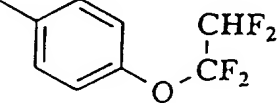
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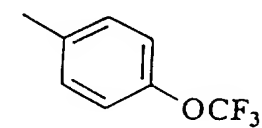
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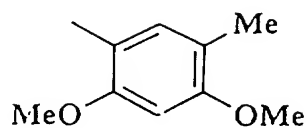
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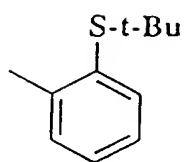
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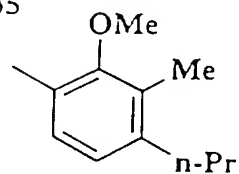
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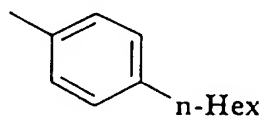
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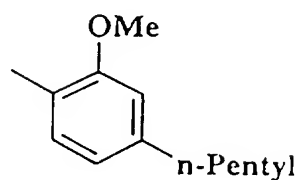
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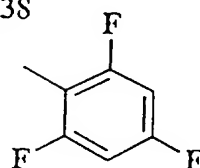
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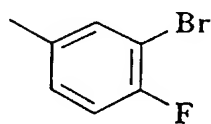
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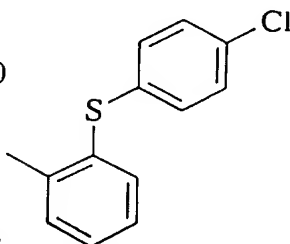
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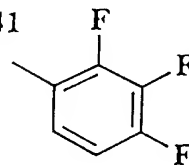
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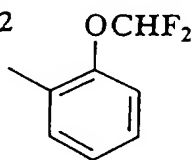
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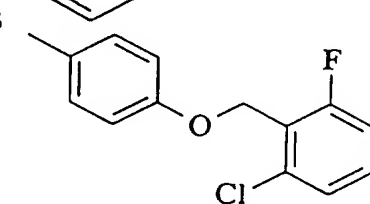
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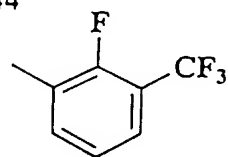
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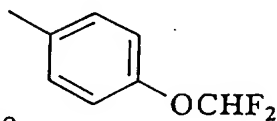
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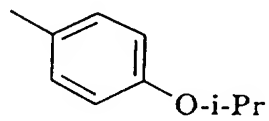
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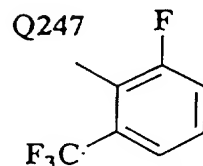
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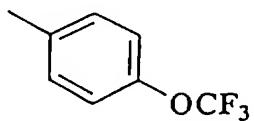
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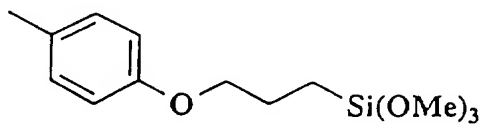
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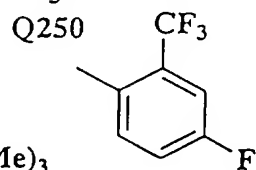
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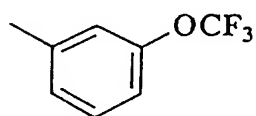
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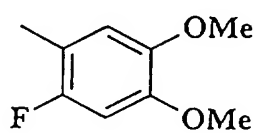
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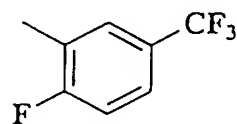
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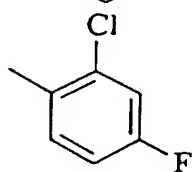
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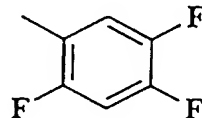
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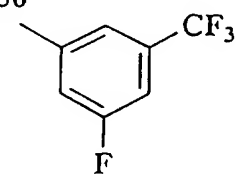
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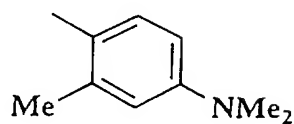
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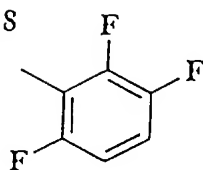
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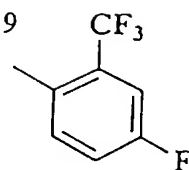
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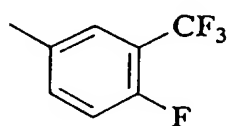
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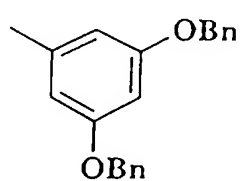
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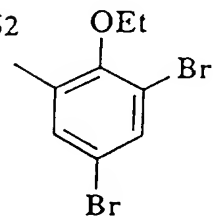
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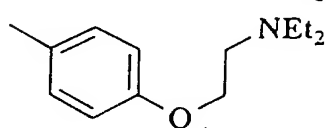
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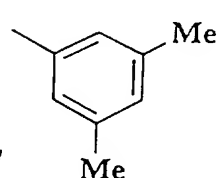
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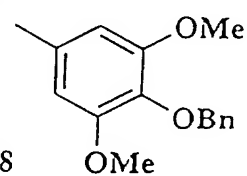
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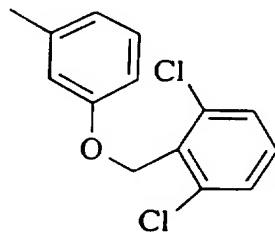
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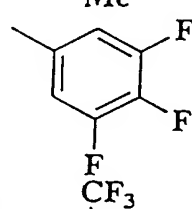
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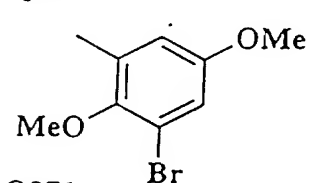
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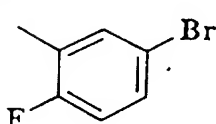
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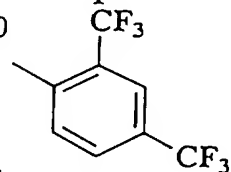
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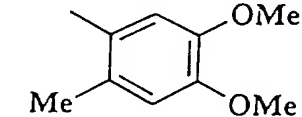
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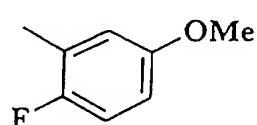
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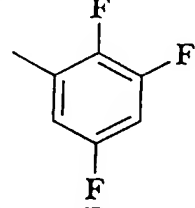
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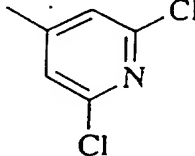
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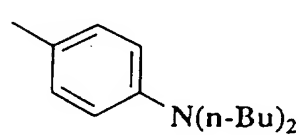
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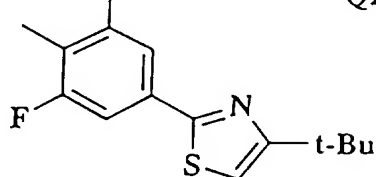
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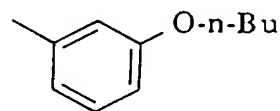
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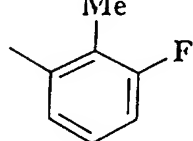
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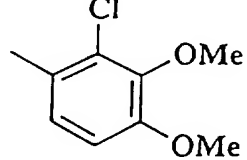
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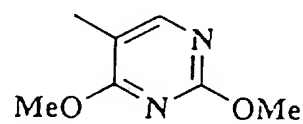
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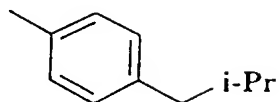
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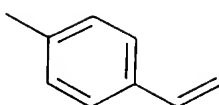
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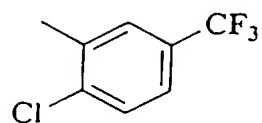
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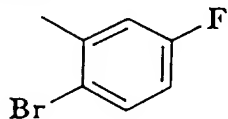
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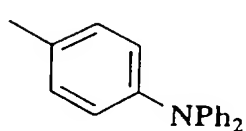
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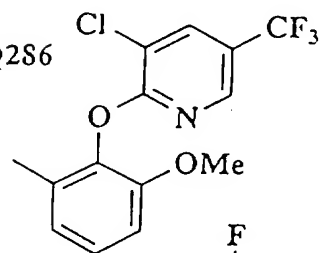
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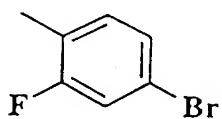
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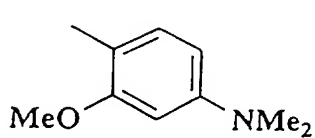
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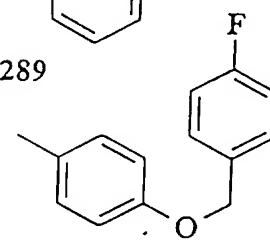
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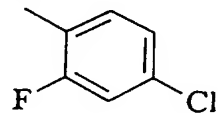
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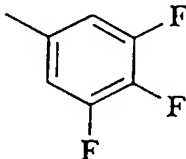
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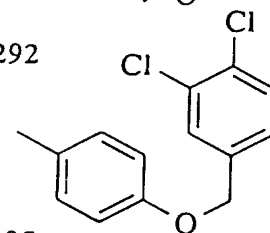
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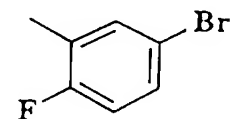
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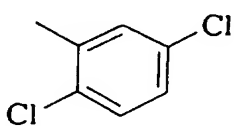
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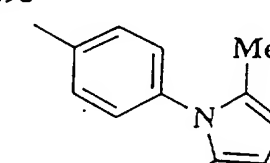
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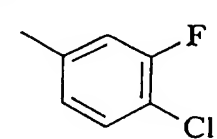
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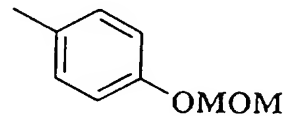
Q295



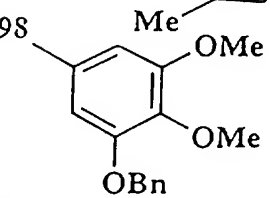
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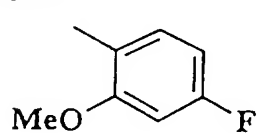
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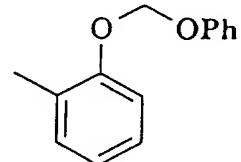
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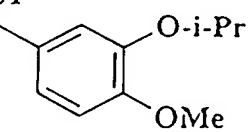
Q299



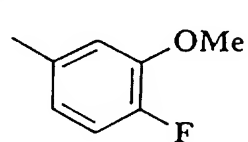
Q300



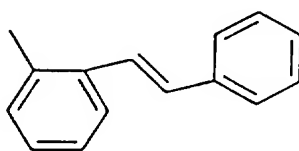
Q301



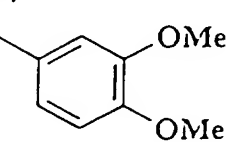
Q302



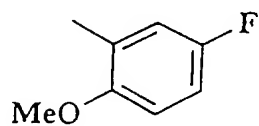
Q303



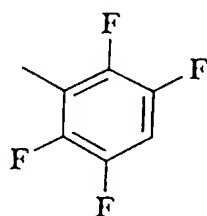
Q304



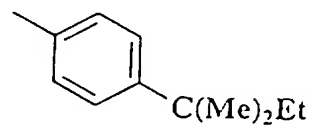
Q305



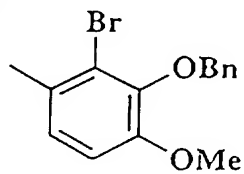
Q306



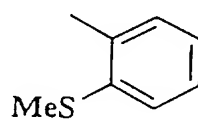
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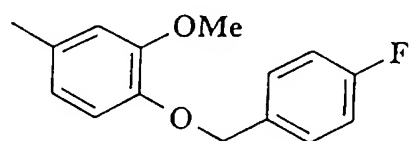
Q308



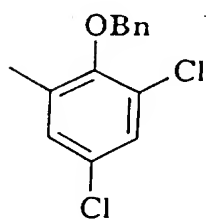
Q309



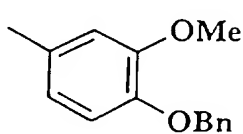
Q310



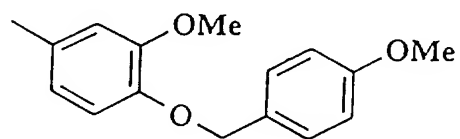
Q311



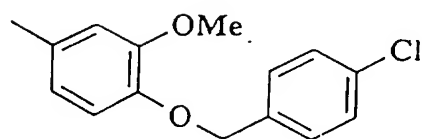
Q312



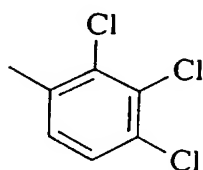
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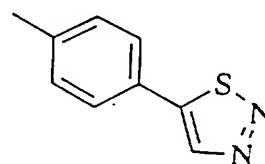
Q314



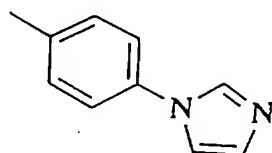
Q315



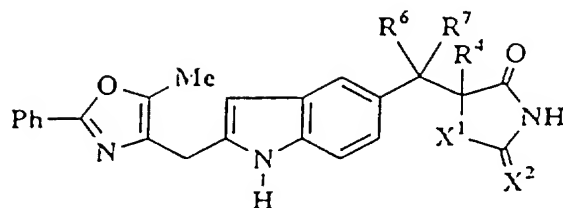
Q316



Q317



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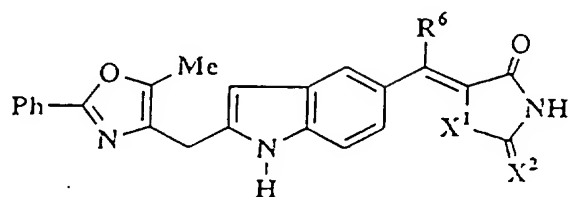


5 In the above formula, X^1 , X^2 , R^4 , R^6 and R^7 are selected from the following Table 1.

Table 1

| | X^1 | X^2 | R^4 | R^6 | R^7 |
|----|-------|-------|-------|-------|-------|
| 10 | S | O | H | H | H |
| | S | S | H | H | H |
| | O | S | H | H | H |
| | O | O | H | H | H |
| 15 | S | O | Me | H | H |
| | S | S | Me | H | H |
| | O | S | Me | H | H |
| | O | O | Me | H | H |
| | S | O | H | H | Me |
| 20 | S | S | H | H | Me |
| | O | S | H | H | Me |
| | O | O | H | H | Me |
| | S | O | Me | H | Me |
| | S | S | Me | H | Me |
| 25 | O | S | Me | H | Me |
| | O | O | Me | H | Me |

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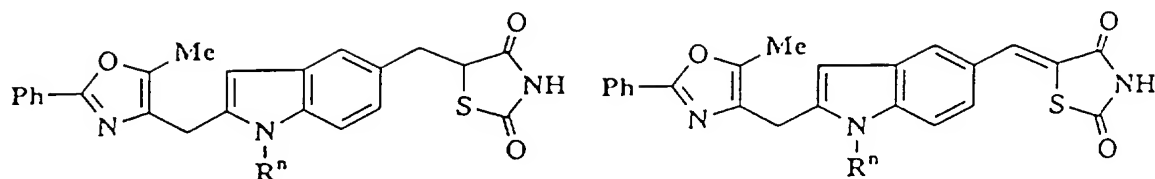


- 5 In the above formula, X^1 , X^2 and R^6 are selected from the following Table 2.

Table 2

| | X^1 | X^2 | R^6 |
|----|-------|-------|-------|
| 10 | S | O | H |
| | S | S | H |
| | O | S | H |
| | O | O | H |
| 15 | S | O | Me |
| | S | S | Me |
| | O | S | Me |
| | O | O | Me |

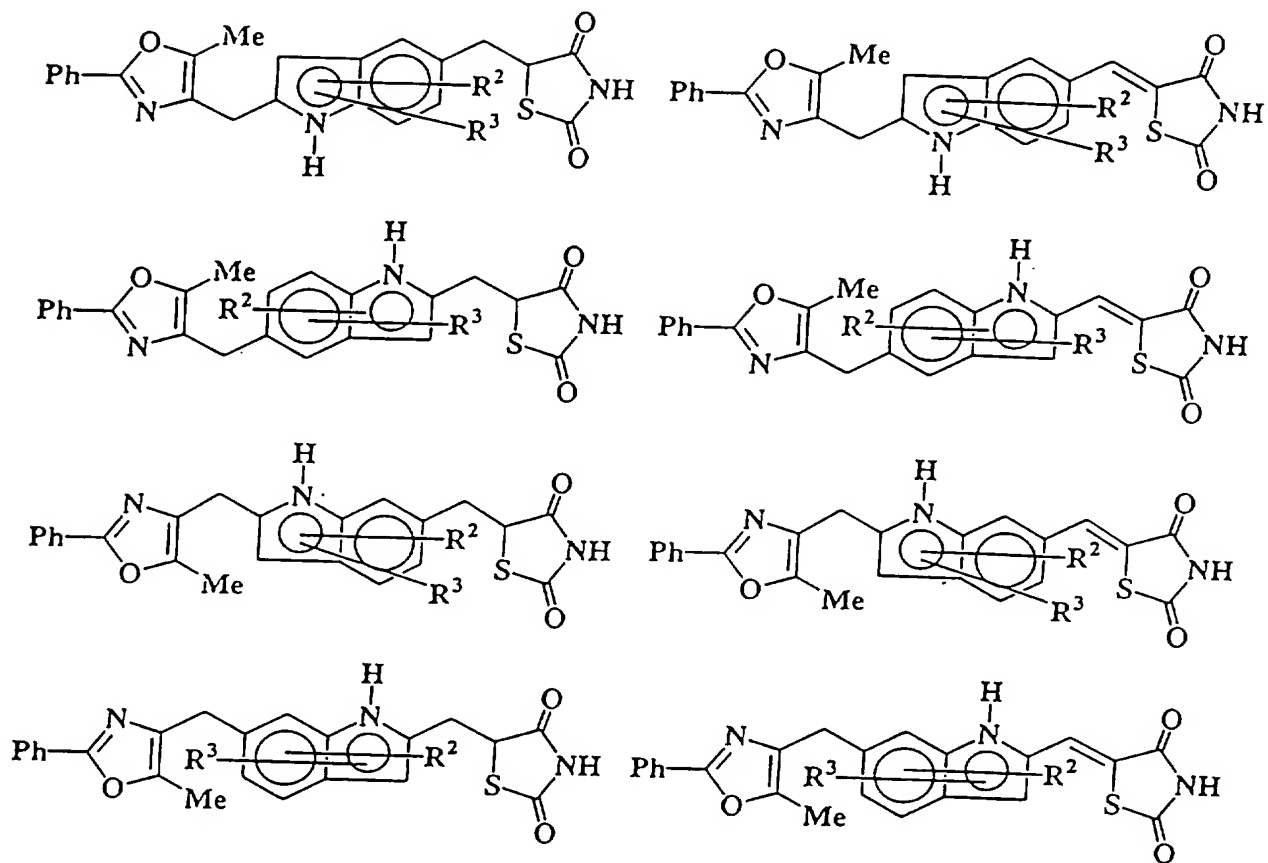
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5 In the above formula, R^n is selected from the following Table 3.

Table 3

| | R^n | R^n |
|----|----------------------|-----------------------|
| 10 | H | benzoyl |
| | Me | methoxycarbonyl |
| | ^nBu | benzyloxycarbonyl |
| | ^nHex | methylcarbamoyl |
| 15 | ^cPr | phenylcarbamoyl |
| | ^cHex | methoxy |
| | methoxymethyl | n-butoxy |
| | benzyloxymethyl | n-hexyloxy |
| | dimethoxyaminomethyl | methoxymethyloxy |
| 20 | acetamidemethyl | triisopropylsilyl |
| | methylthiomethyl | t-butyl diphenylsilyl |
| | carboxyl | methanesulfonyl |
| | formyl | benzenesulfonyl |
| | acetyl | |
| 25 | | |

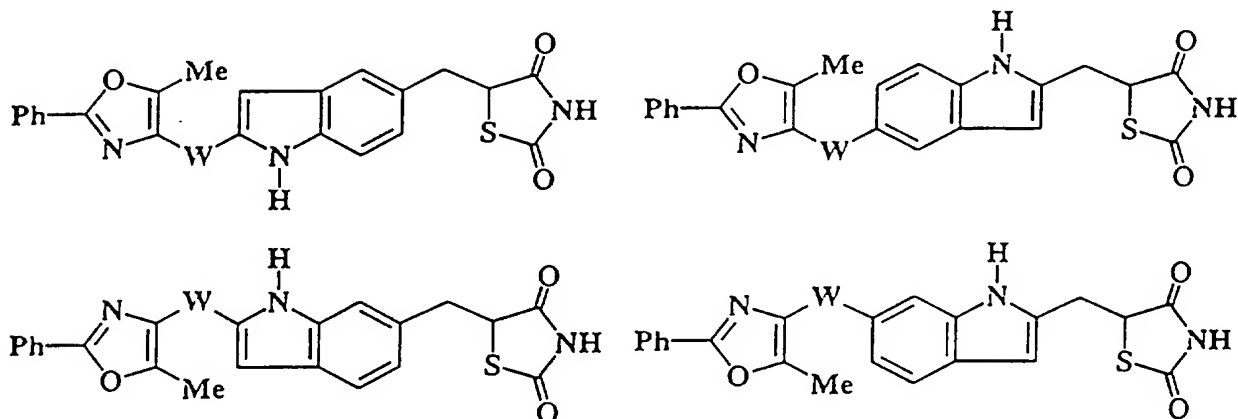


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In the above formula, R^2 and R^3 are selected from the following Table 4.

Table 4

| 5 | <hr/> | |
|-------|-----------------------|-------|
| | R^2 | R^3 |
| 10 | 3-OH | H |
| | 4-OH | H |
| | 6-OH | H |
| | 7-OH | H |
| | 3-Me | H |
| | 3-MeO | H |
| | 3-PhCH ₂ O | H |
| | 3-Ph | H |
| 15 | 3-Cl | H |
| <hr/> | | |

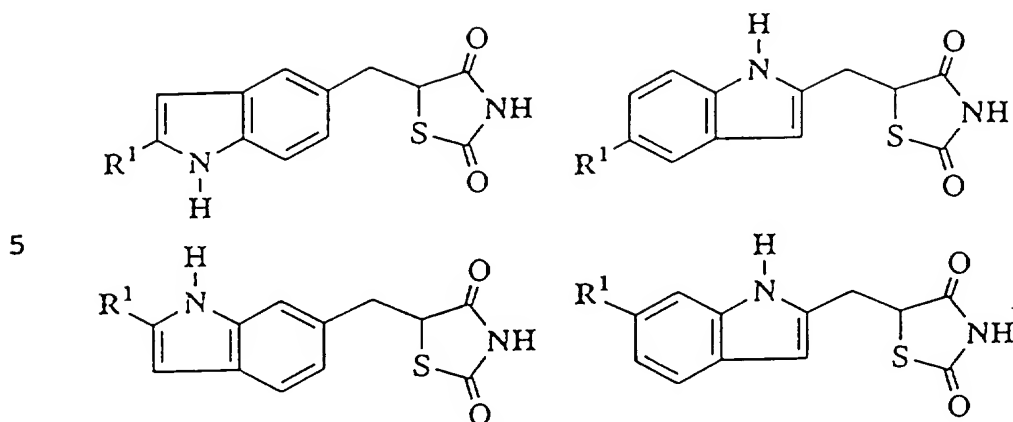


10 In the above formula, W is selected from the following Table 5.

Table 5

| | W | W | W | W |
|----|-----|-----|-----|-----|
| 15 | J1 | J12 | J23 | J34 |
| | J2 | J13 | J24 | J35 |
| | J3 | J14 | J25 | J36 |
| | J4 | J15 | J26 | J37 |
| 20 | J5 | J16 | J27 | J38 |
| | J6 | J17 | J28 | J39 |
| | J7 | J18 | J29 | J40 |
| | J8 | J19 | J30 | J41 |
| | J9 | J20 | J31 | J42 |
| 25 | J10 | J21 | J32 | |
| | J11 | J22 | J33 | |

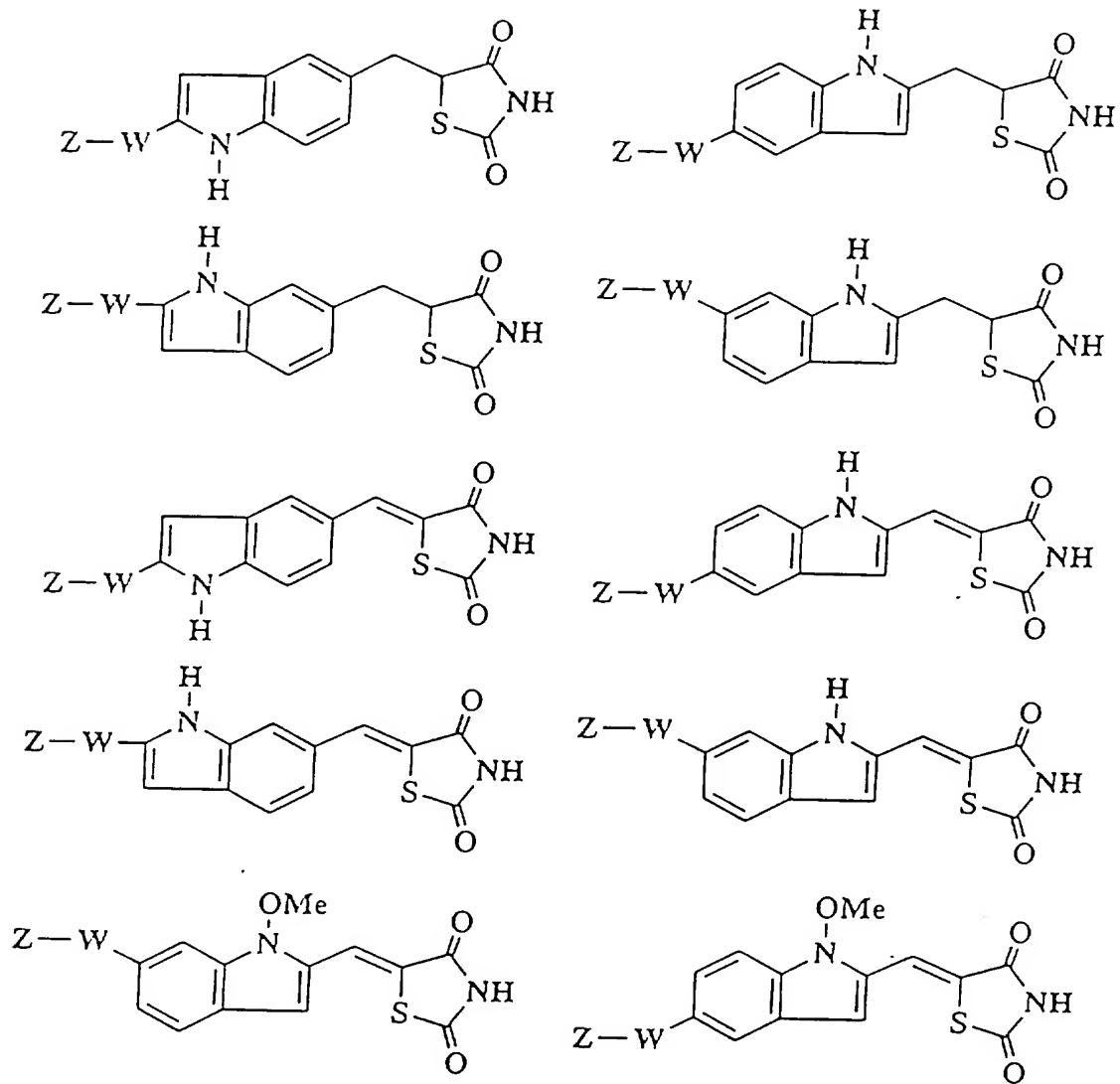
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In the above formula, R¹ is selected from the
 10 following Table 6.

Table 6

| | R ¹ |
|----|-------------------------|
| 15 | n-hexyl |
| | 1-hexenyl |
| | 1-hexynyl |
| | n-hexyloxy |
| | 2-hexenyloxy |
| 20 | n-hexylthio |
| | n-hexylamino |
| | N-methyl-N-n-hexylamino |



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In the above formula, Z and W are selected from the following Tables 7 to 22.

Table 7

| 5 | Z W | | Z W | | Z W | | Z W | |
|----|-----|----|-----|----|-----|----|-----|----|
| | Z | W | Z | W | Z | W | Z | W |
| 10 | Q1 | J1 | Q21 | J1 | Q41 | J1 | Q61 | J1 |
| | Q2 | J1 | Q22 | J1 | Q42 | J1 | Q62 | J1 |
| | Q3 | J1 | Q23 | J1 | Q43 | J1 | Q63 | J1 |
| | Q4 | J1 | Q24 | J1 | Q44 | J1 | Q64 | J1 |
| | Q5 | J1 | Q25 | J1 | Q45 | J1 | Q65 | J1 |
| | Q6 | J1 | Q26 | J1 | Q46 | J1 | Q66 | J1 |
| | Q7 | J1 | Q27 | J1 | Q47 | J1 | Q67 | J1 |
| | Q8 | J1 | Q28 | J1 | Q48 | J1 | Q68 | J1 |
| 15 | Q9 | J1 | Q29 | J1 | Q49 | J1 | Q69 | J1 |
| | Q10 | J1 | Q30 | J1 | Q50 | J1 | Q70 | J1 |
| | Q11 | J1 | Q31 | J1 | Q51 | J1 | Q71 | J1 |
| | Q12 | J1 | Q32 | J1 | Q52 | J1 | Q72 | J1 |
| | Q13 | J1 | Q33 | J1 | Q53 | J1 | Q73 | J1 |
| 20 | Q14 | J1 | Q34 | J1 | Q54 | J1 | Q74 | J1 |
| | Q15 | J1 | Q35 | J1 | Q55 | J1 | Q75 | J1 |
| | Q16 | J1 | Q36 | J1 | Q56 | J1 | Q76 | J1 |
| | Q17 | J1 | Q37 | J1 | Q57 | J1 | Q77 | J1 |
| | Q18 | J1 | Q38 | J1 | Q58 | J1 | Q78 | J1 |
| 25 | Q19 | J1 | Q39 | J1 | Q59 | J1 | Q79 | J1 |
| | Q20 | J1 | Q40 | J1 | Q60 | J1 | Q80 | J1 |

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Table 8

| | Z | W | Z | W | Z | W | Z | W |
|----|------|----|------|----|------|----|------|----|
| 5 | Q81 | J1 | Q101 | J1 | Q121 | J1 | Q141 | J1 |
| | Q82 | J1 | Q102 | J1 | Q122 | J1 | Q142 | J1 |
| | Q83 | J1 | Q103 | J1 | Q123 | J1 | Q143 | J1 |
| | Q84 | J1 | Q104 | J1 | Q124 | J1 | Q144 | J1 |
| | Q85 | J1 | Q105 | J1 | Q125 | J1 | Q145 | J1 |
| 10 | Q86 | J1 | Q106 | J1 | Q126 | J1 | Q146 | J1 |
| | Q87 | J1 | Q107 | J1 | Q127 | J1 | Q147 | J1 |
| | Q88 | J1 | Q108 | J1 | Q128 | J1 | Q148 | J1 |
| | Q89 | J1 | Q109 | J1 | Q129 | J1 | Q149 | J1 |
| | Q90 | J1 | Q110 | J1 | Q130 | J1 | Q150 | J1 |
| 15 | Q91 | J1 | Q111 | J1 | Q131 | J1 | Q151 | J1 |
| | Q92 | J1 | Q112 | J1 | Q132 | J1 | Q152 | J1 |
| | Q93 | J1 | Q113 | J1 | Q133 | J1 | Q153 | J1 |
| | Q94 | J1 | Q114 | J1 | Q134 | J1 | Q154 | J1 |
| | Q95 | J1 | Q115 | J1 | Q135 | J1 | Q155 | J1 |
| 20 | Q96 | J1 | Q116 | J1 | Q136 | J1 | Q156 | J1 |
| | Q97 | J1 | Q117 | J1 | Q137 | J1 | Q157 | J1 |
| | Q98 | J1 | Q118 | J1 | Q138 | J1 | Q158 | J1 |
| | Q99 | J1 | Q119 | J1 | Q139 | J1 | Q159 | J1 |
| | Q100 | J1 | Q120 | J1 | Q140 | J1 | Q160 | J1 |

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Table 9

| | Z | W | Z | W | Z | W | Z | W |
|----|------|----|------|----|------|----|------|----|
| 5 | Q161 | J1 | Q181 | J1 | Q201 | J1 | Q221 | J1 |
| | Q162 | J1 | Q182 | J1 | Q202 | J1 | Q222 | J1 |
| | Q163 | J1 | Q183 | J1 | Q203 | J1 | Q223 | J1 |
| | Q164 | J1 | Q184 | J1 | Q204 | J1 | Q224 | J1 |
| | Q165 | J1 | Q185 | J1 | Q205 | J1 | Q225 | J1 |
| 10 | Q166 | J1 | Q186 | J1 | Q206 | J1 | Q226 | J1 |
| | Q167 | J1 | Q187 | J1 | Q207 | J1 | Q227 | J1 |
| | Q168 | J1 | Q188 | J1 | Q208 | J1 | Q228 | J1 |
| | Q169 | J1 | Q189 | J1 | Q209 | J1 | Q229 | J1 |
| | Q170 | J1 | Q190 | J1 | Q210 | J1 | Q230 | J1 |
| 15 | Q171 | J1 | Q191 | J1 | Q211 | J1 | Q231 | J1 |
| | Q172 | J1 | Q192 | J1 | Q212 | J1 | Q232 | J1 |
| | Q173 | J1 | Q193 | J1 | Q213 | J1 | Q233 | J1 |
| | Q174 | J1 | Q194 | J1 | Q214 | J1 | Q234 | J1 |
| | Q175 | J1 | Q195 | J1 | Q215 | J1 | Q235 | J1 |
| 20 | Q176 | J1 | Q196 | J1 | Q216 | J1 | Q236 | J1 |
| | Q177 | J1 | Q197 | J1 | Q217 | J1 | Q237 | J1 |
| | Q178 | J1 | Q198 | J1 | Q218 | J1 | Q238 | J1 |
| | Q179 | J1 | Q199 | J1 | Q219 | J1 | Q239 | J1 |
| | Q180 | J1 | Q200 | J1 | Q220 | J1 | Q240 | J1 |

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Table 10

| | Z | W | Z | W | Z | W | Z | W |
|----|------|----|------|----|------|----|------|----|
| 5 | Q241 | J1 | Q261 | J1 | Q281 | J1 | Q301 | J1 |
| | Q242 | J1 | Q262 | J1 | Q282 | J1 | Q302 | J1 |
| | Q243 | J1 | Q263 | J1 | Q283 | J1 | Q303 | J1 |
| | Q244 | J1 | Q264 | J1 | Q284 | J1 | Q304 | J1 |
| | Q245 | J1 | Q265 | J1 | Q285 | J1 | Q305 | J1 |
| 10 | Q246 | J1 | Q266 | J1 | Q286 | J1 | Q306 | J1 |
| | Q247 | J1 | Q267 | J1 | Q287 | J1 | Q307 | J1 |
| | Q248 | J1 | Q268 | J1 | Q288 | J1 | Q308 | J1 |
| | Q249 | J1 | Q269 | J1 | Q289 | J1 | Q309 | J1 |
| | Q250 | J1 | Q270 | J1 | Q290 | J1 | Q310 | J1 |
| 15 | Q251 | J1 | Q271 | J1 | Q291 | J1 | Q311 | J1 |
| | Q252 | J1 | Q272 | J1 | Q292 | J1 | Q312 | J1 |
| | Q253 | J1 | Q273 | J1 | Q293 | J1 | Q313 | J1 |
| | Q254 | J1 | Q274 | J1 | Q294 | J1 | Q314 | J1 |
| | Q255 | J1 | Q275 | J1 | Q295 | J1 | Q315 | J1 |
| 20 | Q256 | J1 | Q276 | J1 | Q296 | J1 | Q316 | J1 |
| | Q257 | J1 | Q277 | J1 | Q297 | J1 | Q317 | J1 |
| | Q258 | J1 | Q278 | J1 | Q298 | J1 | | |
| | Q259 | J1 | Q279 | J1 | Q299 | J1 | | |
| | Q260 | J1 | Q280 | J1 | Q300 | J1 | | |

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Table 11

| | Z | W | Z | W | Z | W | Z | W |
|----|-----|----|-----|----|-----|----|-----|----|
| 5 | Q1 | J2 | Q21 | J2 | Q41 | J2 | Q61 | J2 |
| | Q2 | J2 | Q22 | J2 | Q42 | J2 | Q62 | J2 |
| | Q3 | J2 | Q23 | J2 | Q43 | J2 | Q63 | J2 |
| | Q4 | J2 | Q24 | J2 | Q44 | J2 | Q64 | J2 |
| | Q5 | J2 | Q25 | J2 | Q45 | J2 | Q65 | J2 |
| 10 | Q6 | J2 | Q26 | J2 | Q46 | J2 | Q66 | J2 |
| | Q7 | J2 | Q27 | J2 | Q47 | J2 | Q67 | J2 |
| | Q8 | J2 | Q28 | J2 | Q48 | J2 | Q68 | J2 |
| | Q9 | J2 | Q29 | J2 | Q49 | J2 | Q69 | J2 |
| | Q10 | J2 | Q30 | J2 | Q50 | J2 | Q70 | J2 |
| 15 | Q11 | J2 | Q31 | J2 | Q51 | J2 | Q71 | J2 |
| | Q12 | J2 | Q32 | J2 | Q52 | J2 | Q72 | J2 |
| | Q13 | J2 | Q33 | J2 | Q53 | J2 | Q73 | J2 |
| | Q14 | J2 | Q34 | J2 | Q54 | J2 | Q74 | J2 |
| | Q15 | J2 | Q35 | J2 | Q55 | J2 | Q75 | J2 |
| 20 | Q16 | J2 | Q36 | J2 | Q56 | J2 | Q76 | J2 |
| | Q17 | J2 | Q37 | J2 | Q57 | J2 | Q77 | J2 |
| | Q18 | J2 | Q38 | J2 | Q58 | J2 | Q78 | J2 |
| | Q19 | J2 | Q39 | J2 | Q59 | J2 | Q79 | J2 |
| | Q20 | J2 | Q40 | J2 | Q60 | J2 | Q80 | J2 |

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Table 12

| | Z | W | Z | W | Z | W | Z | W |
|----|---------|---------|---------|---------|---|---|---|---|
| 5 | Q81 J2 | Q101 J2 | Q121 J2 | Q141 J2 | | | | |
| | Q82 J2 | Q102 J2 | Q122 J2 | Q142 J2 | | | | |
| | Q83 J2 | Q103 J2 | Q123 J2 | Q143 J2 | | | | |
| | Q84 J2 | Q104 J2 | Q124 J2 | Q144 J2 | | | | |
| | Q85 J2 | Q105 J2 | Q125 J2 | Q145 J2 | | | | |
| 10 | Q86 J2 | Q106 J2 | Q126 J2 | Q146 J2 | | | | |
| | Q87 J2 | Q107 J2 | Q127 J2 | Q147 J2 | | | | |
| | Q88 J2 | Q108 J2 | Q128 J2 | Q148 J2 | | | | |
| | Q89 J2 | Q109 J2 | Q129 J2 | Q149 J2 | | | | |
| | Q90 J2 | Q110 J2 | Q130 J2 | Q150 J2 | | | | |
| 15 | Q91 J2 | Q111 J2 | Q131 J2 | Q151 J2 | | | | |
| | Q92 J2 | Q112 J2 | Q132 J2 | Q152 J2 | | | | |
| | Q93 J2 | Q113 J2 | Q133 J2 | Q153 J2 | | | | |
| | Q94 J2 | Q114 J2 | Q134 J2 | Q154 J2 | | | | |
| | Q95 J2 | Q115 J2 | Q135 J2 | Q155 J2 | | | | |
| 20 | Q96 J2 | Q116 J2 | Q136 J2 | Q156 J2 | | | | |
| | Q97 J2 | Q117 J2 | Q137 J2 | Q157 J2 | | | | |
| | Q98 J2 | Q118 J2 | Q138 J2 | Q158 J2 | | | | |
| | Q99 J2 | Q119 J2 | Q139 J2 | Q159 J2 | | | | |
| | Q100 J2 | Q120 J2 | Q140 J2 | Q160 J2 | | | | |

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Table 13

| | Z | W | Z | W | Z | W | Z | W |
|----|------|----|------|----|------|----|------|----|
| 5 | Q161 | J2 | Q181 | J2 | Q201 | J2 | Q221 | J2 |
| | Q162 | J2 | Q182 | J2 | Q202 | J2 | Q222 | J2 |
| | Q163 | J2 | Q183 | J2 | Q203 | J2 | Q223 | J2 |
| | Q164 | J2 | Q184 | J2 | Q204 | J2 | Q224 | J2 |
| | Q165 | J2 | Q185 | J2 | Q205 | J2 | Q225 | J2 |
| 10 | Q166 | J2 | Q186 | J2 | Q206 | J2 | Q226 | J2 |
| | Q167 | J2 | Q187 | J2 | Q207 | J2 | Q227 | J2 |
| | Q168 | J2 | Q188 | J2 | Q208 | J2 | Q228 | J2 |
| | Q169 | J2 | Q189 | J2 | Q209 | J2 | Q229 | J2 |
| | Q170 | J2 | Q190 | J2 | Q210 | J2 | Q230 | J2 |
| 15 | Q171 | J2 | Q191 | J2 | Q211 | J2 | Q231 | J2 |
| | Q172 | J2 | Q192 | J2 | Q212 | J2 | Q232 | J2 |
| | Q173 | J2 | Q193 | J2 | Q213 | J2 | Q233 | J2 |
| | Q174 | J2 | Q194 | J2 | Q214 | J2 | Q234 | J2 |
| | Q175 | J2 | Q195 | J2 | Q215 | J2 | Q235 | J2 |
| 20 | Q176 | J2 | Q196 | J2 | Q216 | J2 | Q236 | J2 |
| | Q177 | J2 | Q197 | J2 | Q217 | J2 | Q237 | J2 |
| | Q178 | J2 | Q198 | J2 | Q218 | J2 | Q238 | J2 |
| | Q179 | J2 | Q199 | J2 | Q219 | J2 | Q239 | J2 |
| | Q180 | J2 | Q200 | J2 | Q220 | J2 | Q240 | J2 |

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Table 14

| | Z | W | Z | W | Z | W | Z | W |
|----|------|----|------|----|------|----|------|----|
| 5 | Q241 | J2 | Q261 | J2 | Q281 | J2 | Q301 | J2 |
| | Q242 | J2 | Q262 | J2 | Q282 | J2 | Q302 | J2 |
| | Q243 | J2 | Q263 | J2 | Q283 | J2 | Q303 | J2 |
| | Q244 | J2 | Q264 | J2 | Q284 | J2 | Q304 | J2 |
| | Q245 | J2 | Q265 | J2 | Q285 | J2 | Q305 | J2 |
| 10 | Q246 | J2 | Q266 | J2 | Q286 | J2 | Q306 | J2 |
| | Q247 | J2 | Q267 | J2 | Q287 | J2 | Q307 | J2 |
| | Q248 | J2 | Q268 | J2 | Q288 | J2 | Q308 | J2 |
| | Q249 | J2 | Q269 | J2 | Q289 | J2 | Q309 | J2 |
| | Q250 | J2 | Q270 | J2 | Q290 | J2 | Q310 | J2 |
| 15 | Q251 | J2 | Q271 | J2 | Q291 | J2 | Q311 | J2 |
| | Q252 | J2 | Q272 | J2 | Q292 | J2 | Q312 | J2 |
| | Q253 | J2 | Q273 | J2 | Q293 | J2 | Q313 | J2 |
| | Q254 | J2 | Q274 | J2 | Q294 | J2 | Q314 | J2 |
| | Q255 | J2 | Q275 | J2 | Q295 | J2 | Q315 | J2 |
| 20 | Q256 | J2 | Q276 | J2 | Q296 | J2 | Q316 | J2 |
| | Q257 | J2 | Q277 | J2 | Q297 | J2 | Q317 | J2 |
| | Q258 | J2 | Q278 | J2 | Q298 | J2 | | |
| | Q259 | J2 | Q279 | J2 | Q299 | J2 | | |
| | Q260 | J2 | Q280 | J2 | Q300 | J2 | | |

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Table 15

| | Z | W | Z | W | Z | W | Z | W |
|----|-----|----|-----|----|-----|----|-----|----|
| 5 | Q1 | J4 | Q21 | J4 | Q41 | J4 | Q61 | J4 |
| | Q2 | J4 | Q22 | J4 | Q42 | J4 | Q62 | J4 |
| | Q3 | J4 | Q23 | J4 | Q43 | J4 | Q63 | J4 |
| | Q4 | J4 | Q24 | J4 | Q44 | J4 | Q64 | J4 |
| | Q5 | J4 | Q25 | J4 | Q45 | J4 | Q65 | J4 |
| 10 | Q6 | J4 | Q26 | J4 | Q46 | J4 | Q66 | J4 |
| | Q7 | J4 | Q27 | J4 | Q47 | J4 | Q67 | J4 |
| | Q8 | J4 | Q28 | J4 | Q48 | J4 | Q68 | J4 |
| | Q9 | J4 | Q29 | J4 | Q49 | J4 | Q69 | J4 |
| | Q10 | J4 | Q30 | J4 | Q50 | J4 | Q70 | J4 |
| 15 | Q11 | J4 | Q31 | J4 | Q51 | J4 | Q71 | J4 |
| | Q12 | J4 | Q32 | J4 | Q52 | J4 | Q72 | J4 |
| | Q13 | J4 | Q33 | J4 | Q53 | J4 | Q73 | J4 |
| | Q14 | J4 | Q34 | J4 | Q54 | J4 | Q74 | J4 |
| | Q15 | J4 | Q35 | J4 | Q55 | J4 | Q75 | J4 |
| 20 | Q16 | J4 | Q36 | J4 | Q56 | J4 | Q76 | J4 |
| | Q17 | J4 | Q37 | J4 | Q57 | J4 | Q77 | J4 |
| | Q18 | J4 | Q38 | J4 | Q58 | J4 | Q78 | J4 |
| | Q19 | J4 | Q39 | J4 | Q59 | J4 | Q79 | J4 |
| | Q20 | J4 | Q40 | J4 | Q60 | J4 | Q80 | J4 |

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Table 16

| | Z | W | Z | W | Z | W | Z | W |
|----|------|----|------|----|------|----|------|----|
| 5 | Q81 | J4 | Q101 | J4 | Q121 | J4 | Q141 | J4 |
| | Q82 | J4 | Q102 | J4 | Q122 | J4 | Q142 | J4 |
| | Q83 | J4 | Q103 | J4 | Q123 | J4 | Q143 | J4 |
| | Q84 | J4 | Q104 | J4 | Q124 | J4 | Q144 | J4 |
| | Q85 | J4 | Q105 | J4 | Q125 | J4 | Q145 | J4 |
| 10 | Q86 | J4 | Q106 | J4 | Q126 | J4 | Q146 | J4 |
| | Q87 | J4 | Q107 | J4 | Q127 | J4 | Q147 | J4 |
| | Q88 | J4 | Q108 | J4 | Q128 | J4 | Q148 | J4 |
| | Q89 | J4 | Q109 | J4 | Q129 | J4 | Q149 | J4 |
| | Q90 | J4 | Q110 | J4 | Q130 | J4 | Q150 | J4 |
| 15 | Q91 | J4 | Q111 | J4 | Q131 | J4 | Q151 | J4 |
| | Q92 | J4 | Q112 | J4 | Q132 | J4 | Q152 | J4 |
| | Q93 | J4 | Q113 | J4 | Q133 | J4 | Q153 | J4 |
| | Q94 | J4 | Q114 | J4 | Q134 | J4 | Q154 | J4 |
| | Q95 | J4 | Q115 | J4 | Q135 | J4 | Q155 | J4 |
| 20 | Q96 | J4 | Q116 | J4 | Q136 | J4 | Q156 | J4 |
| | Q97 | J4 | Q117 | J4 | Q137 | J4 | Q157 | J4 |
| | Q98 | J4 | Q118 | J4 | Q138 | J4 | Q158 | J4 |
| | Q99 | J4 | Q119 | J4 | Q139 | J4 | Q159 | J4 |
| | Q100 | J4 | Q120 | J4 | Q140 | J4 | Q160 | J4 |

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Table 17

| | Z | W | Z | W | Z | W | Z | W |
|----|------|----|------|----|------|----|------|----|
| 5 | Q161 | J4 | Q181 | J4 | Q201 | J4 | Q221 | J4 |
| | Q162 | J4 | Q182 | J4 | Q202 | J4 | Q222 | J4 |
| | Q163 | J4 | Q183 | J4 | Q203 | J4 | Q223 | J4 |
| | Q164 | J4 | Q184 | J4 | Q204 | J4 | Q224 | J4 |
| | Q165 | J4 | Q185 | J4 | Q205 | J4 | Q225 | J4 |
| 10 | Q166 | J4 | Q186 | J4 | Q206 | J4 | Q226 | J4 |
| | Q167 | J4 | Q187 | J4 | Q207 | J4 | Q227 | J4 |
| | Q168 | J4 | Q188 | J4 | Q208 | J4 | Q228 | J4 |
| | Q169 | J4 | Q189 | J4 | Q209 | J4 | Q229 | J4 |
| | Q170 | J4 | Q190 | J4 | Q210 | J4 | Q230 | J4 |
| 15 | Q171 | J4 | Q191 | J4 | Q211 | J4 | Q231 | J4 |
| | Q172 | J4 | Q192 | J4 | Q212 | J4 | Q232 | J4 |
| | Q173 | J4 | Q193 | J4 | Q213 | J4 | Q233 | J4 |
| | Q174 | J4 | Q194 | J4 | Q214 | J4 | Q234 | J4 |
| | Q175 | J4 | Q195 | J4 | Q215 | J4 | Q235 | J4 |
| 20 | Q176 | J4 | Q196 | J4 | Q216 | J4 | Q236 | J4 |
| | Q177 | J4 | Q197 | J4 | Q217 | J4 | Q237 | J4 |
| | Q178 | J4 | Q198 | J4 | Q218 | J4 | Q238 | J4 |
| | Q179 | J4 | Q199 | J4 | Q219 | J4 | Q239 | J4 |
| | Q180 | J4 | Q200 | J4 | Q220 | J4 | Q240 | J4 |

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Table 18

| | Z | W | Z | W | Z | W | Z | W |
|----|------|----|------|----|------|----|------|----|
| 5 | Q241 | J4 | Q261 | J4 | Q281 | J4 | Q301 | J4 |
| | Q242 | J4 | Q262 | J4 | Q282 | J4 | Q302 | J4 |
| | Q243 | J4 | Q263 | J4 | Q283 | J4 | Q303 | J4 |
| | Q244 | J4 | Q264 | J4 | Q284 | J4 | Q304 | J4 |
| | Q245 | J4 | Q265 | J4 | Q285 | J4 | Q305 | J4 |
| 10 | Q246 | J4 | Q266 | J4 | Q286 | J4 | Q306 | J4 |
| | Q247 | J4 | Q267 | J4 | Q287 | J4 | Q307 | J4 |
| | Q248 | J4 | Q268 | J4 | Q288 | J4 | Q308 | J4 |
| | Q249 | J4 | Q269 | J4 | Q289 | J4 | Q309 | J4 |
| | Q250 | J4 | Q270 | J4 | Q290 | J4 | Q310 | J4 |
| 15 | Q251 | J4 | Q271 | J4 | Q291 | J4 | Q311 | J4 |
| | Q252 | J4 | Q272 | J4 | Q292 | J4 | Q312 | J4 |
| | Q253 | J4 | Q273 | J4 | Q293 | J4 | Q313 | J4 |
| | Q254 | J4 | Q274 | J4 | Q294 | J4 | Q314 | J4 |
| | Q255 | J4 | Q275 | J4 | Q295 | J4 | Q315 | J4 |
| 20 | Q256 | J4 | Q276 | J4 | Q296 | J4 | Q316 | J4 |
| | Q257 | J4 | Q277 | J4 | Q297 | J4 | Q317 | J4 |
| | Q258 | J4 | Q278 | J4 | Q298 | J4 | | |
| | Q259 | J4 | Q279 | J4 | Q299 | J4 | | |
| | Q260 | J4 | Q280 | J4 | Q300 | J4 | | |
| 25 | | | | | | | | |

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Table 19

| | Z | W | Z | W | Z | W | Z | W |
|----|-----|----|-----|----|-----|----|-----|----|
| 5 | Q1 | J5 | Q21 | J5 | Q41 | J5 | Q61 | J5 |
| | Q2 | J5 | Q22 | J5 | Q42 | J5 | Q62 | J5 |
| | Q3 | J5 | Q23 | J5 | Q43 | J5 | Q63 | J5 |
| | Q4 | J5 | Q24 | J5 | Q44 | J5 | Q64 | J5 |
| | Q5 | J5 | Q25 | J5 | Q45 | J5 | Q65 | J5 |
| 10 | Q6 | J5 | Q26 | J5 | Q46 | J5 | Q66 | J5 |
| | Q7 | J5 | Q27 | J5 | Q47 | J5 | Q67 | J5 |
| | Q8 | J5 | Q28 | J5 | Q48 | J5 | Q68 | J5 |
| | Q9 | J5 | Q29 | J5 | Q49 | J5 | Q69 | J5 |
| | Q10 | J5 | Q30 | J5 | Q50 | J5 | Q70 | J5 |
| 15 | Q11 | J5 | Q31 | J5 | Q51 | J5 | Q71 | J5 |
| | Q12 | J5 | Q32 | J5 | Q52 | J5 | Q72 | J5 |
| | Q13 | J5 | Q33 | J5 | Q53 | J5 | Q73 | J5 |
| | Q14 | J5 | Q34 | J5 | Q54 | J5 | Q74 | J5 |
| | Q15 | J5 | Q35 | J5 | Q55 | J5 | Q75 | J5 |
| 20 | Q16 | J5 | Q36 | J5 | Q56 | J5 | Q76 | J5 |
| | Q17 | J5 | Q37 | J5 | Q57 | J5 | Q77 | J5 |
| | Q18 | J5 | Q38 | J5 | Q58 | J5 | Q78 | J5 |
| | Q19 | J5 | Q39 | J5 | Q59 | J5 | Q79 | J5 |
| | Q20 | J5 | Q40 | J5 | Q60 | J5 | Q80 | J5 |

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Table 20

| | Z | W | Z | W | Z | W | Z | W |
|----|---------|---------|---------|---------|---|---|---|---|
| 5 | Q81 J5 | Q101 J5 | Q121 J5 | Q141 J5 | | | | |
| | Q82 J5 | Q102 J5 | Q122 J5 | Q142 J5 | | | | |
| | Q83 J5 | Q103 J5 | Q123 J5 | Q143 J5 | | | | |
| | Q84 J5 | Q104 J5 | Q124 J5 | Q144 J5 | | | | |
| | Q85 J5 | Q105 J5 | Q125 J5 | Q145 J5 | | | | |
| 10 | Q86 J5 | Q106 J5 | Q126 J5 | Q146 J5 | | | | |
| | Q87 J5 | Q107 J5 | Q127 J5 | Q147 J5 | | | | |
| | Q88 J5 | Q108 J5 | Q128 J5 | Q148 J5 | | | | |
| | Q89 J5 | Q109 J5 | Q129 J5 | Q149 J5 | | | | |
| | Q90 J5 | Q110 J5 | Q130 J5 | Q150 J5 | | | | |
| 15 | Q91 J5 | Q111 J5 | Q131 J5 | Q151 J5 | | | | |
| | Q92 J5 | Q112 J5 | Q132 J5 | Q152 J5 | | | | |
| | Q93 J5 | Q113 J5 | Q133 J5 | Q153 J5 | | | | |
| | Q94 J5 | Q114 J5 | Q134 J5 | Q154 J5 | | | | |
| | Q95 J5 | Q115 J5 | Q135 J5 | Q155 J5 | | | | |
| 20 | Q96 J5 | Q116 J5 | Q136 J5 | Q156 J5 | | | | |
| | Q97 J5 | Q117 J5 | Q137 J5 | Q157 J5 | | | | |
| | Q98 J5 | Q118 J5 | Q138 J5 | Q158 J5 | | | | |
| | Q99 J5 | Q119 J5 | Q139 J5 | Q159 J5 | | | | |
| | Q100 J5 | Q120 J5 | Q140 J5 | Q160 J5 | | | | |

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Table 21

| | Z | W | Z | W | Z | W | Z | W |
|----|------|----|------|----|------|----|------|----|
| 5 | Q161 | J5 | Q181 | J5 | Q201 | J5 | Q221 | J5 |
| | Q162 | J5 | Q182 | J5 | Q202 | J5 | Q222 | J5 |
| | Q163 | J5 | Q183 | J5 | Q203 | J5 | Q223 | J5 |
| | Q164 | J5 | Q184 | J5 | Q204 | J5 | Q224 | J5 |
| | Q165 | J5 | Q185 | J5 | Q205 | J5 | Q225 | J5 |
| 10 | Q166 | J5 | Q186 | J5 | Q206 | J5 | Q226 | J5 |
| | Q167 | J5 | Q187 | J5 | Q207 | J5 | Q227 | J5 |
| | Q168 | J5 | Q188 | J5 | Q208 | J5 | Q228 | J5 |
| | Q169 | J5 | Q189 | J5 | Q209 | J5 | Q229 | J5 |
| | Q170 | J5 | Q190 | J5 | Q210 | J5 | Q230 | J5 |
| 15 | Q171 | J5 | Q191 | J5 | Q211 | J5 | Q231 | J5 |
| | Q172 | J5 | Q192 | J5 | Q212 | J5 | Q232 | J5 |
| | Q173 | J5 | Q193 | J5 | Q213 | J5 | Q233 | J5 |
| | Q174 | J5 | Q194 | J5 | Q214 | J5 | Q234 | J5 |
| | Q175 | J5 | Q195 | J5 | Q215 | J5 | Q235 | J5 |
| 20 | Q176 | J5 | Q196 | J5 | Q216 | J5 | Q236 | J5 |
| | Q177 | J5 | Q197 | J5 | Q217 | J5 | Q237 | J5 |
| | Q178 | J5 | Q198 | J5 | Q218 | J5 | Q238 | J5 |
| | Q179 | J5 | Q199 | J5 | Q219 | J5 | Q239 | J5 |
| | Q180 | J5 | Q200 | J5 | Q220 | J5 | Q240 | J5 |
| 25 | | | | | | | | |

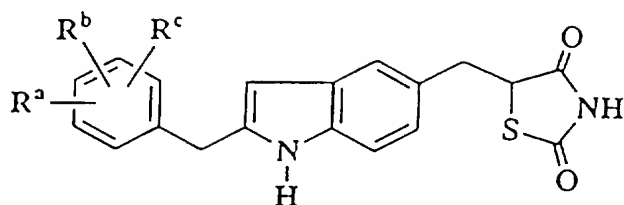
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Table 22

| | Z | W | Z | W | Z | W | Z | W |
|----|------|----|------|----|------|----|------|----|
| 5 | Q241 | J5 | Q261 | J5 | Q281 | J5 | Q301 | J5 |
| | Q242 | J5 | Q262 | J5 | Q282 | J5 | Q302 | J5 |
| | Q243 | J5 | Q263 | J5 | Q283 | J5 | Q303 | J5 |
| | Q244 | J5 | Q264 | J5 | Q284 | J5 | Q304 | J5 |
| | Q245 | J5 | Q265 | J5 | Q285 | J5 | Q305 | J5 |
| 10 | Q246 | J5 | Q266 | J5 | Q286 | J5 | Q306 | J5 |
| | Q247 | J5 | Q267 | J5 | Q287 | J5 | Q307 | J5 |
| | Q248 | J5 | Q268 | J5 | Q288 | J5 | Q308 | J5 |
| | Q249 | J5 | Q269 | J5 | Q289 | J5 | Q309 | J5 |
| | Q250 | J5 | Q270 | J5 | Q290 | J5 | Q310 | J5 |
| 15 | Q251 | J5 | Q271 | J5 | Q291 | J5 | Q311 | J5 |
| | Q252 | J5 | Q272 | J5 | Q292 | J5 | Q312 | J5 |
| | Q253 | J5 | Q273 | J5 | Q293 | J5 | Q313 | J5 |
| | Q254 | J5 | Q274 | J5 | Q294 | J5 | Q314 | J5 |
| | Q255 | J5 | Q275 | J5 | Q295 | J5 | Q315 | J5 |
| 20 | Q256 | J5 | Q276 | J5 | Q296 | J5 | Q316 | J5 |
| | Q257 | J5 | Q277 | J5 | Q297 | J5 | Q317 | J5 |
| | Q258 | J5 | Q278 | J5 | Q298 | J5 | | |
| | Q259 | J5 | Q279 | J5 | Q299 | J5 | | |
| | Q260 | J5 | Q280 | J5 | Q300 | J5 | | |

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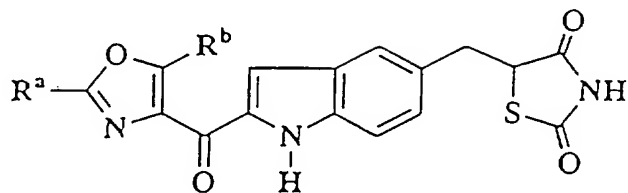
5

In the above formula, R^a , R^b and R^c are selected from the following Table 23.

Table 23

| | R^a | R^b | R^c | R^a | R^b | R^c |
|----|-------|-------|-------|-------------------|-------|-------|
| 10 | 2-Me | H | H | 4-Q83 | H | H |
| | 3-Me | H | H | 2-OH | H | H |
| | 4-Me | H | H | 3-OH | H | H |
| 15 | 2-OMe | H | H | 4-OH | H | H |
| | 3-OMe | H | H | 2-F | H | H |
| | 4-OMe | H | H | 3-F | H | H |
| | 2-Ph | H | H | 4-F | H | H |
| | 3-Ph | H | H | 2-Cl | H | H |
| 20 | 4-Ph | H | H | 3-Cl | H | H |
| | 4-Q11 | H | H | 4-Cl | H | H |
| | 4-Q18 | H | H | 2-Br | H | H |
| | 4-Q19 | H | H | 3-Br | H | H |
| | 4-Q49 | H | H | 4-Br | H | H |
| 25 | 4-Q13 | H | H | 3-CF ₃ | H | H |
| | 4-OPh | H | H | | | |

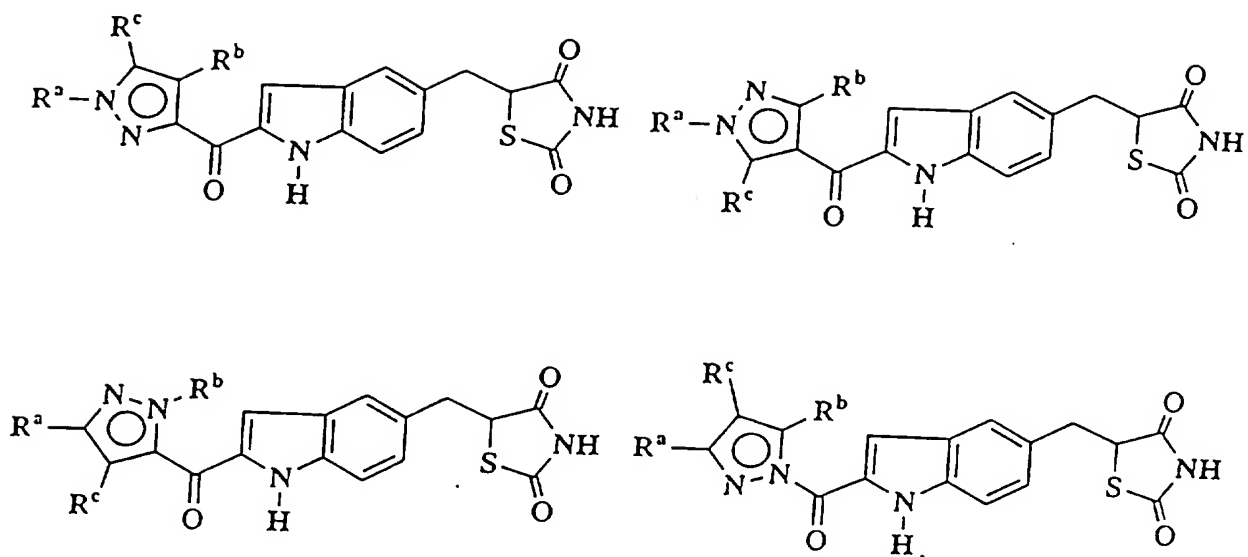
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- 5 In the above formula, R^a , R^b and R^c are selected from the following Table 24.

Table 24

| | R^a | R^b | R^a | R^b | R^a | R^b |
|----|---------|-------|---------|-------|-------|---------|
| 10 | H | Me | Q6 | Me | Q14 | Me |
| | Me | Me | Q85 | Me | Q49 | Me |
| | Et | Me | Q86 | Me | Q76 | Me |
| | n Pr | Me | Q87 | Me | Q13 | Me |
| 15 | i Pr | Me | Q10 | Me | OPh | Me |
| | t Bu | Me | Q88 | Me | Q83 | Me |
| | c Pr | Me | Q89 | Me | Ph | H |
| | c Hex | Me | Q8 | Me | Ph | Me |
| | Q84 | Me | Q90 | Me | Ph | Et |
| 20 | Ph | Me | Q91 | Me | Ph | n Pr |
| | Q1 | Me | 4-Ph-Ph | Me | Ph | i Pr |
| | Q2 | Me | Q11 | Me | Ph | t Bu |
| | Q3 | Me | Q12 | Me | Ph | c Pr |
| | Q4 | Me | Q18 | Me | Ph | c Hex |
| 25 | Q5 | Me | Q19 | Me | Ph | Ph |



In the above formula, R^a , R^b and R^c are selected from the following Table 25.

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Table 25

| | R ^a | R ^b | R ^c | R ^a | R ^b | R ^c |
|----|------------------|----------------|----------------|----------------|------------------|----------------|
| 5 | H | Me | H | Q90 | Me | H |
| | Me | Me | H | Q91 | Me | H |
| | Et | Me | H | 4-Ph-Ph | Me | H |
| | ⁿ Pr | Me | H | Q11 | Me | H |
| | ⁱ Pr | Me | H | Q12 | Me | H |
| 10 | ^t Bu | Me | H | Q18 | Me | H |
| | ^c Pr | Me | H | Q19 | Me | H |
| | ^c Hex | Me | H | Q14 | Me | H |
| | Q84 | Me | H | Q49 | Me | H |
| | Ph | Me | H | Q76 | Me | H |
| 15 | Q1 | Me | H | Q13 | Me | H |
| | Q2 | Me | H | OPh | Me | H |
| | Q3 | Me | H | Q83 | Me | H |
| | Q4 | Me | H | Ph | H | H |
| | Q5 | Me | H | Ph | Me | H |
| 20 | Q6 | Me | H | Ph | Et | H |
| | Q85 | Me | H | Ph | ⁿ Pr | H |
| | Q86 | Me | H | Ph | ⁱ Pr | H |
| | Q87 | Me | H | Ph | ^t Bu | H |
| | Q10 | Me | H | Ph | ^c Pr | H |
| 25 | Q88 | Me | H | Ph | ^c Hex | H |
| | Q89 | Me | H | Ph | Ph | H |
| | Q8 | Me | H | Ph | Me | Me |

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As evident from the following test results, the compound (I) or its pharmaceutically acceptable salt of the present invention has a hypoglycemic activity, and can be used alone or in a mixture with a known
5 pharmaceutically acceptable binder, excipient, lubricant or disintegrator, for preventing or treating diabetes mellitus of mammals including humans, mice, rats, rabbits, dogs, monkeys, cows, horses, pigs and the like. The compound (I) or its pharmaceutically acceptable salt
10 of the present invention can also be used for preventing or treating diabetic complications including diabetic eye diseases (such as diabetic cataract and diabetic retinopathy), diabetic neuropathy, diabetic nephropathy, diabetic gangrene, and the like. The compound (I) or its
15 pharmaceutically acceptable salt of the present invention can also be used in combination with various oral hypoglycemic agents such as insulin derivatives, sulfonylurea derivatives and biguanide derivatives, and aldose-reductase inhibitory agents.

20 The compounds (I) of the present invention may be formulated into various suitable formulations depending upon the manner of administration. The compounds of the present invention may be administered in the form of free thiazolidindione or in the form of physiologically
25 hydrolyzable and acceptable pharmaceutically acceptable salts (such as sodium salts or potassium salts).

The pharmaceutical composition of the present

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invention is preferably administered orally in the form of the compound of the present invention by itself or in the form of powders, granules, tablets or capsules formulated by mixing the compound of the present
5 invention with a suitable pharmaceutically acceptable carrier including a binder (such as hydroxypropyl cellulose, syrup, gum arabic, gelatin, sorbitol, tragacanth gum, polyvinyl pyrrolidone or CMC-Ca), an excipient (such as lactose, sugar, corn starch, calcium
10 phosphate, sorbitol, glycine or microcrystal cellulose powder), a lubricant (such as magnesium stearate, talc, polyethylene glycol or silica), and a disintegrator (such as potato starch).

However, the pharmaceutical composition of the
15 present invention is not limited to such oral administration and it is applicable for parenteral administration. For example, it may be administered in the form of e.g. a suppository formulated by using oily base material such as cacao butter, polyethylene glycol,
20 lanolin or fatty acid triglyceride, a transdermal therapeutic base formulated by using liquid paraffin, white vaseline, a higher alcohol, Macrogol ointment, hydrophilic ointment or hydro-gel base material, an injection formulation formulated by using one or more
25 materials selected from the group consisting of polyethylene glycol, hydro-gel base material, distilled water, distilled water for injection and an excipient

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such as lactose or corn starch, or a formulation for administration through mucous membranes such as an ocular mucous membrane, a nasal mucous membrane and an oral mucous membrane.

5 The daily dose of the compound of the present invention is from 0.05 to 50 mg, preferably from 0.1 to 10 mg per kg weight of a patient, and it is administered from once to three times per day. The dose may of course be varied depending upon the age, the weight or the
10 condition of illness of a patient.

EXAMPLES

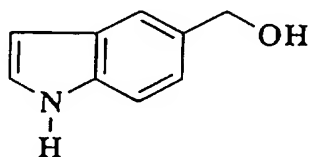
Now, the present invention will be described in further detail with reference to Examples for preparation of the compounds of the present invention,
15 Pharmacological Test Examples and Formulation Examples. However, it should be understood that the present invention is by no means restricted by such specific Examples.

Reference 1 Synthesis of hydroxymethylindole (Compound
20 (III))

Synthesis Route 1

Synthesis of 5-hydroxymethylindole (III-1)

25



(III-1)

10.60 g (65.77 mmol) of 5-indolecarboxylic acid was

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dissolved in 120 ml of tetrahydrofuran, and was cooled to 0°C. To the resultant mixture, 9.98 g (263.09 mmol) of lithium aluminum hydride was added little by little. After gradually rising reaction temperature to room temperature, a resultant mixture was heated under reflux for 30 minutes. To the resultant reaction mixture, were added little by little Celite, ethyl acetate, methanol and water in this order, and the mixture was quenched with an excess amount of a reducing agent. A resultant reaction mixture was filtrated by means of a small amount of silica gel. The solvent in the filtrate was removed by distillation under reduced pressure to obtain a 9.50 g (98.1%) of the subject compound (III-1).

Colorless plate-like crystals

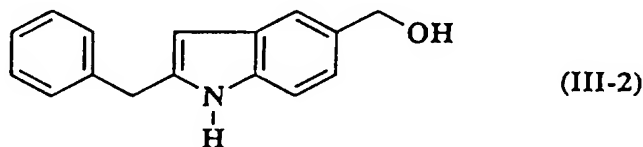
Melting point: 58-58.5°C (solvent for recrystallization: diethylether/hexane)

60MHz ¹H-NMR(CDCl₃), δ : 2.10(1H, brs), 4.60(2H, s), 6.35(1H, dd, J=4.0, 3.0Hz), 6.80-7.30(3H, m), 7.41(1H, brs), 8.22(1H, brs).

MS(EI) m/e: 147(M⁺), 130, 118.

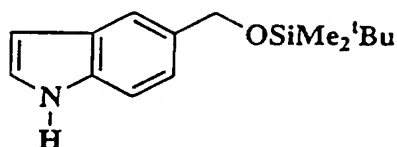
Synthesis route 2

Synthesis of 2-benzyl-5-hydroxymethylindole (III-2)



- 174 -

5-t-butyltrimethylsilyloxymethylindole (Compound (VII-1))



(VII-1)

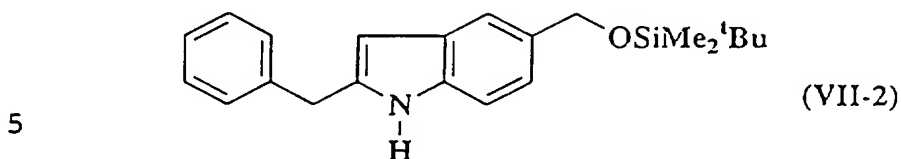
5

9.50 g (65.55 mmol) of Compound (III-1) was dissolved in 40 ml of dimethylformamide dehydrated with molecular sieves, and 6.96 g (98.325 mmol) of imidazole and 11.85 g (78.66 mmol) of t-butyltrimethylsilyl chloride were added thereto and were stirred at room temperature for 10 hours. After finishing the reaction, a saturated sodium chloride aqueous solution was added to the reaction solution, and the mixture was extracted with ethyl acetate to obtain an organic phase which was then washed with a saturated sodium chloride aqueous solution. The washed organic phase was then dried with anhydrous sodium sulfate, and the residue obtained after removing a solvent by distillation under reduced pressure was subjected to silica gel column chromatography (eluent: ethyl acetate/hexane=1/4). The product thus obtained was further recrystallized to obtain 13.05 g of the subject compound (VII-1).

Colorless plate-like crystals
Melting point: 48-49°C (solvent used for recrystallization: diethylether/hexane)
60MHz ¹H-NMR(CDCl₃), δ: 0.10(6H, s), 0.92(9H, s), 4.75(2H, s), 6.40(1H, d, J=4.0, 3.0Hz), 6.92-7.35(3H, m), 7.45(1H, brs), 8.00(1H, brs).
MS(EI) m/e: 261(M⁺), 246, 204, 130.

- 175 -

2-benzyl-5-t-butyldimethylsilyloxymethylindole (Compound (VII-2))



To an anhydrous tetrahydrofuran (5 ml) solution of 555.5 mg (2.1248 mmol) of Compound (VII-1), was dropwise added 1.3 ml (2.1248 mmol) of butyl lithium (1.6 M hexane solution) at -78°C, and the resultant mixture was stirred for 15 minutes. Dry carbon dioxide gas was passed through the reaction solution for 15 minutes. After fully removing carbon dioxide gas at a reaction temperature of 20°C, the reaction temperature was lowered to -78°C. After fully cooling, 2.8 ml (4.2496 mmol) of t-butyl lithium (1.54 M solution in pentane) was dropwise added thereto, and the resultant mixture was stirred for 2 hours. Thereafter, an anhydrous tetrahydrofuran (2 ml) solution of 726.9 mg (4.2496 mmol) of benzylbromide (Compound (VIII-1)) was added thereto at room temperature. After stirring the reaction mixture at -78°C for 30 minutes, the reaction mixture was further stirred at room temperature for 30 minutes and further stirred at a refluxing temperature of a solvent for 15 minutes. After terminating the reaction by adding methylene chloride and 2M hydrochloric acid to the reaction solution, an organic phase obtained was washed

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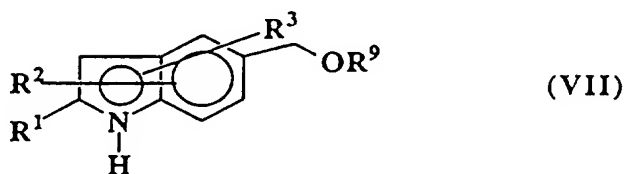
with a saturated ammonium chloride aqueous solution. After drying the organic phase thus obtained with anhydrous sodium sulfate, a residue obtained after removing a solvent by distillation under reduced pressure
5 was subjected to silica gel column chromatography (eluent: ethyl acetate/hexane = 1/4) and was repeatedly subjected to a silica gel column chromatography (eluent: ethyl acetate/hexane = 1/15) to obtain 111.9 mg (15.0%) of the subject compound (VII-2).

10 Yellow oily material

60MHz ¹H-NMR(CDCl₃), δ:0.10(6H, s), 0.92(9H, s), 4.00(2H, s), 4.72(2H, s), 6.18(1H, d, J=2.0Hz), 6.90-7.30(2H, m), 7.38(1H, brs), 7.51(1H, brs).MS (EI) m/e:351(M⁺), 294, 235, 220, 149.

In the same manner as above, electrophilic reagents
15 (Compound (VIII)) were used to Compound (VII-1) in place of benzylbromide to synthesize the following compounds (R¹, R² and R³ in the table correspond to the substituents of Compound (VII)).

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5

(Rⁿ=H, R¹=W-Z, R⁹=SiMe₂Bu^t)

10

| Compound No. | R ¹ | R ² | R ³ | Electrophile (VIII) | Properties (mp °C) |
|--------------|----------------|----------------|----------------|---------------------|--------------------------------|
| VII-3 | | H | H | | Colorless needles (104-105) |
| VII-4 | | H | H | | Yellow crystals (135-138) |

15 Compound (VII-3)

60MHz ¹H-NMR(CDCl₃), δ : 0.90(6H, s), 0.92(9H, s), 2.27(3H, s), 3.96(2H, s), 4.75(2H, s), 6.21(1H, d, J=2.0Hz), 6.90-7.70(6H, m), 7.75-8.15(2H, m), 8.77(1H, brs).

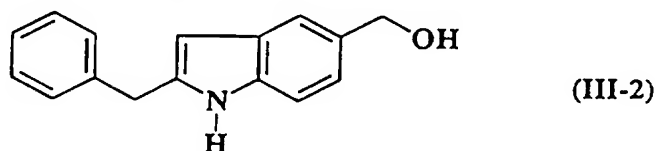
MS(EI) m/e: 432(M⁺), 417, 375, 301, 156, 105, 75.

20 Compound (VII-4)

60MHz ¹H-NMR(CDCl₃), δ : 1.12(6H, s), 1.95(9H, s), 2.68(3H, s), 4.75(2H, s), 7.00-8.30(9H, m), 9.32(1H, brs).

MS(FD) m/e: 446.

25 2-benzyl-5-hydroxymethylindole (Compound (III-2))



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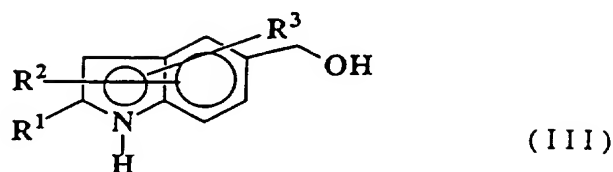
To a tetrahydrofuran (5 ml) solution of 111.9 mg (0.3183 mmol) of Compound (VII-2), was added a tetrahydrofuran (1 ml) solution of 166.4 mg (2.041 mmol) of tetra-n-butylammonium fluoride. After stirring the resultant mixture at room temperature for 3 hours, 166.4 mg (2.041 mmol) of tetra-n-butyl ammonium fluoride was further added thereto and was stirred at room temperature for 2 hours. The resultant reaction solution was extracted by adding 2M-hydrochloric acid, water and chloroform. An organic phase obtained was dried with anhydrous sodium sulfate, and a residue obtained after removing a solvent under reduced pressure was subjected to silica gel column chromatography (eluent: ethyl acetate/hexane = 1/1) to obtain 57.7 mg (76.4%) of the subject compound (III-2).

Yellow crystals

60MHz ¹H-NMR(CDCl₃), δ : 1.75(1H, s), 4.00(2H, s), 4.62(1H, s), 6.20(1H, d, J=2.0Hz), 7.00-7.35(2H, m), 7.39(1H, brs), 7.83(1H, brs).

In the same manner as above, Compound (VII-3 and VII-4) were used to synthesize the following compounds (R¹, R² and R³ in the Table correspond to the substituents of Compound (III)).

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5

(Rⁿ=H, R¹=W-Z)

10

| Compound No. | R ¹ | R ² | R ³ | Properties (mp °C) |
|--------------|----------------|----------------|----------------|-------------------------------|
| III-3 | | H | H | Pale yellow needles (104-105) |
| III-4 | | H | H | Pale yellow needles (225-226) |

Compound (III-3)

60MHz ¹H-NMR(CDCl₃), δ: 2.09(1H, brs), 2.22(3H, s), 3.89(2H, s), 4.62(2H, s), 6.18(1H, brs), 6.80-7.60(6H, m), 7.70-8.10(2H, m), 8.92(1H, brs).

MS(EI) m/e:318(M⁺), 301, 287, 275, 172, 147, 130, 115, 105, 77.

Compound (III-4)

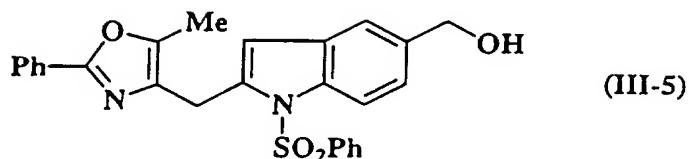
500MHz ¹H-NMR(DMSO-d₆), δ: 2.65(3H, s), 4.58(2H, d, J=5.6Hz), 5.15(1H, t, J=5.6Hz), 7.31(1H, dd, J=8.5, 1.0Hz), 7.48(1H, d, J=8.5Hz), 7.53(1H, t, J=7.3Hz), 7.66(2H, t, J=7.3Hz), 7.73(1H, s), 7.96(1H, d, J=1.0Hz), 8.20(2H, d, J=7.3Hz), 11.92(1H, brs).

MS(EI) m/e:332(M⁺), 315, 301, 285, 186, 174, 156, 144, 128, 117, 91, 77.

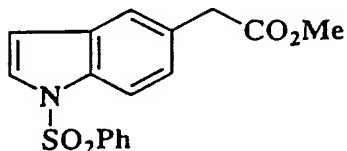
Synthesis Route 3

25 Synthesis of 1-benzenesulfonyl-5-hydroxymethyl-2-(2-phenyl-5-methyloxazole-4-yl) methylindole (Compound III-5)

- 180 -



5 Methyl 5-(1-benzenesulfonyl)indolecarboxylate



10 1.0470 g (6.4966 mmol) of 5-indolecarboxylic acid was dissolved in 10 ml of acetone and was reacted with an excess amount of diazomethane at room temperature. After finishing the reaction, a residue obtained by removing a solvent under reduced pressure was subjected to silica
15 column chromatography (eluent: ethyl acetate/hexane = 1/2) to obtain 1.1123 g (97.7%) of methyl 5-indolecarboxylate.

Colorless crystals

60MHz ¹H-NMR(CDCl₃), δ : 3.78(3H, s), 6.52(1H, dd, J=3.0, 3.0Hz), 7.12(1H, d, J=3.0Hz), 7.28(1H, d, J=9.0Hz), 7.82(1H, dd, J=9.0, 2.0Hz), 8.30(1H, d, J=2.0Hz), 8.51(1H, brs).

MS(EI) m/e: 175(M)⁺, 149, 144, 116.

67.8 mg (2.8262 mmol) of sodium hydride was suspended in 2 ml of dimethylformamide dehydrated with molecular
25 sieves. To the suspension thus obtained, was added a molecular sieves-dehydrated dimethylformaldehyde (5 ml) solution of 412.6 mg (2.3552 mmol) of methyl 5-

- 181 -

indolecarboxylate at room temperature. After stirring the resultant mixture for 40 minutes, a molecular sieves-dehydrated dimethylformaldehyde (2 ml) solution of 832.0 mg (4.7104 mmol) of benzenesulfonyl chloride was added thereto at room temperature and was stirred for 2 hours. Water was added to the reaction solution and the reaction solution was extracted with ethyl acetate to obtain an organic phase which was then washed with a saturated sodium chloride aqueous solution. The washed organic phase was dried with anhydrous sodium sulfate, and a residue obtained by removing a solvent under reduced pressure was washed with hexane to obtain 729.9 mg (98.3%) of the aimed methyl 5-(1-benzenesulfonyl)indolecarboxylate.

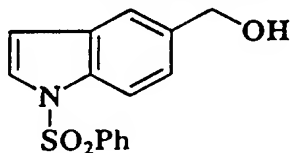
Colorless crystals

Melting point: 149-149.5°C (solvent used for recrystallization: benzene)

60MHz ¹H-NMR (CDCl₃), δ : 3.90(3H, s), 6.67(1H, d, J=5.0Hz), 7.20-8.40(9H, m).

MS(EI) m/e: 315(M⁺), 284, 174, 159, 143, 115.

1-benzenesulfonyl-5-hydroxymethylindole



508.7 mg (1.6131 mmol) of methyl 5-(1-benzenesulfonyl)indolecarboxylate was dissolved in 5 ml of tetrahydrofuran dehydrated with molecular sieves and

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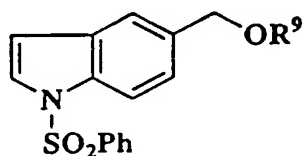
6.32 ml (3.2263 mmol) of diisobutylaluminium hydride (1.02 M toluene solution) was gradually dropwise added thereto at room temperature and the resultant mixture was stirred at room temperature for 30 minutes. To the resultant reaction solution, were added Celite, water and ethylacetate in this order, and the resultant reaction solution was filtrated by a filter paper and the filtrate was washed with a saturated sodium chloride aqueous solution. An organic phase obtained was dried with anhydrous sodium sulfate, and a residue obtained by removing a solvent under reduced pressure was then filtrated by silica gel to obtain 508.8 mg of aimed material. The compound thus obtained was used in the following reaction without further purifying.

Colorless oily material

60MHz $^1\text{H-NMR}(\text{CDCl}_3)$, δ : 4.65(2H, brs), 6.55(1H, d, $J=5.0\text{Hz}$), 7.00-8.10(9H, m).

MS(EI) m/e : 287(M^+), 270, 141, 129, 118, 91, 77.

1-benzenesulfonyl-5-t-butyl dimethylsilyloxymethylindole
(Compound (VII-5))



(VII-5)
($R^n = \text{SO}_2\text{Ph}$,
 $R^9 = \text{SiMe}_2\text{Bu}^t$)

508.8 mg (1.6131 mmol) of 1-benzenesulfonyl-5-hydroxymethylindole was dissolved in 5 ml of dimethylformamide dehydrated with molecular sieves, and

- 183 -

164.7 mg (2.4197 mmol) of imidazole and 486.2 mg (3.2262 mmol) of t-butyldimethylsilyl chloride were added thereto and the resultant mixture was stirred at room temperature for 16 hours. After finishing the reaction, the

5 saturated sodium chloride aqueous solution was added to the resultant reaction solution and the resultant reaction solution was extracted with ethyl acetate to obtain an organic phase which was then washed with a saturated sodium chloride aqueous solution. The organic

10 phase thus obtained was dried with anhydrous sodium sulfate, and a residue obtained by removing a solvent under reduced pressure was subjected to a silica gel column chromatography (eluent: ethyl acetate/hexane = 1/4) to obtain 611.9 mg (94.5%) of the subject compound

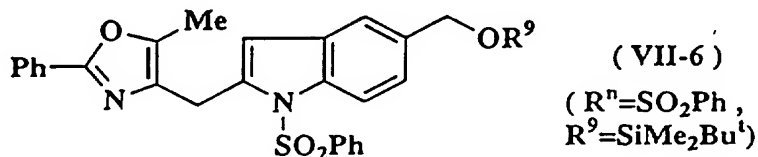
15 (VII-5)

Colorless oily material

60MHz ¹H-NMR(CDCl₃), δ : 0.07(6H, s), 0.90(9H, s), 4.70(2H, s), 7.00-8.00 (9H, m).

1-benzenesulfonyl-2-(2-phenyl-5-methyloxazole-4-yl)methyl-5-t-butyldimethylsilyloxymethylindole (Compound

20 (VII-6))



25

To an anhydrous tetrahydrofuran (2 ml) solution of 167.1 mg (0.4161 mmol) of Compound (VII-5), was dropwise

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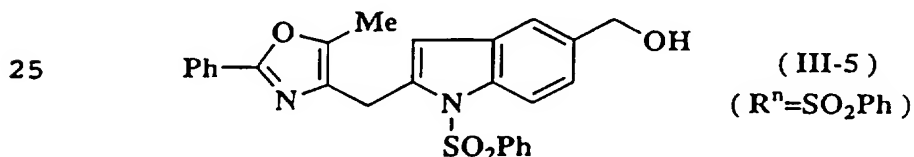
added 0.35 ml (0.5409 mmol) of t-butyllithium (1.54 M solution in pentane) at -12°C. After rising the reaction temperature to room temperature, the reaction mixture was stirred for 30 minutes, and 248.9 mg (0.8322 mmol) of 2-phenyl-5-methyloxazole-4-ylmethyl iodide (Compound (VIII-2)) and anhydrous tetrahydrofuran (2 ml) solution were added thereto at room temperature. After stirring the mixture for 1 hour, water was added to the reaction solution and the reaction solution was extracted with ethyl acetate to obtain an organic phase which was then washed with a saturated sodium chloride aqueous solution. The organic phase thus obtained was dried with anhydrous sodium sulfate, and a residue obtained by removing a solvent under reduced pressure was subjected to a silica gel column chromatography (eluent: ethyl acetate/hexane = 1/7) repeatedly to obtain 160.9 mg (67.5%) of the subject compound (VII-6).

Light-yellow oily material

60MHz ¹H-NMR(CDCl₃), δ: 0.12(6H, s), 0.90(9H, s), 2.22(3H, s), 4.22(2H, s), 4.72(2H, s), 6.27(1H, s), 6.80-8.20(13H, m).

MS(EI) m/e: 572(M⁺), 515, 441, 374, 299, 105.

1-benzenesulfonyl-2-(2-phenyl-5-methyloxazole-4-yl)methyl-5-hydroxymethylindole (Compound (III-5))



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To a tetrahydrofuran (1 ml) solution of 46.9 mg (0.0819 mmol) of Compound (VII-6), was added 0.5 ml of tetran-butylammonium fluoride (1M THF solution). After stirring the resultant mixture for 1 hour at room temperature, the water was added to the resultant reaction solution and the reaction solution was extracted with chloroform. An organic phase obtained was dried with anhydrous sodium sulfate, and a residue obtained by removing a solvent under reduced pressure was subjected to silica gel column chromatography (eluent: ethyl acetate/hexane = 1/2) to obtain quantitatively 39.5 mg of the subject compound (III-5).
Light-yellow oily material

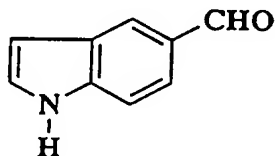
60MHz ¹H-NMR(CDCl₃), δ:3.22(3H, s), 4.22(2H, s), 4.66(2H, s), 6.28(1H, s), 6.80-8.30(13H, m).

MS(EI) m/e:458(M⁺), 317, 300, 287, 245, 217, 195, 154, 105, 77.

Reference Example 2 Synthesis of formylindole (Compound II)

Synthesis Route 1

Synthesis of 5-formylindole (II-a-1)



(II-a-1)

750.2 mg (5.0971 mmol) of 5-hydroxymethylindole (Compound (III-1)) was dissolved in 14 ml of

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tetrahydrofuran, and 4.4314 g (50.971 mmol) of activated manganese dioxide was added thereto and the resultant mixture was heat-refluxed for 17 hours. After the reaction mixture was filtrated to remove an oxidizing agent residue, yellow brown crystals (657.0 mg) obtained were subjected to silica gel column chromatography (eluent: ethyl acetate/hexane = 1/1) to obtain 602.6 mg (81.4%) of the subject compound (II-a-1)

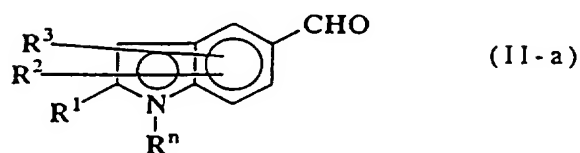
Light yellow crystals Melting point: 95-96°C

10 60MHz ¹H-NMR(CDCl₃), δ :6.50(1H, dd, J=3.0, 2.0Hz), 7.18(1H, d, J=3.0Hz), 7.36(1H, d, J=9.0Hz), 7.68(1H, dd, J=9.0, 1.0Hz), 8.05(1H, brs), 8.75(1H, brs), 9.90(1H s).

MS(EI) m/e:145(M)⁺, 116, 89.

15 In the same manner as above, the following compounds were synthesized (R¹, R², R³ and Rⁿ in the table correspond to the substituents of Compound (II)).

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| Compound No. | R ¹ | R ² | R ³ | R ⁿ | Starting material (III) | Properties (mp °C) |
|--------------|----------------|----------------|----------------|--------------------|-------------------------|----------------------------------|
| II-a-2 | 2-(Ph-) | H | H | H | III-2 | Yellow crystals (108-109) |
| II-a-3 | 2-(Ph-) | H | H | H | III-3 | Pale yellow crystals (127-128) |
| II-a-4 | 2-(Ph-) | H | H | H | III-4 | Pale yellow powder (258.5-259.5) |
| II-a-5 | 2-(Ph-) | H | H | SO ₂ Ph | III-5 | Yellow amorphous |

Compound (II-a-2)

60MHz ¹H-NMR(CDCl₃), δ : 4.08(2H, s), 6.36(1H, brs), 6.88-7.50(6H, m), 7.58(1H, dd, J=9.0, 2.0Hz), 7.97(1H, brs), 8.30(1H, brs), 9.85(1H, s).

MS(EI) m/e: 235(M⁺), 206, 158, 129, 115, 102, 91, 77.

Compound (II-a-3)

60MHz ¹H-NMR(CDCl₃), δ : 2.27(3H, s), 3.92(2H, s), 6.35(1H, brs), 7.10-8.05(8H, m), 9.55(1H, brs), 9.81(1H, s).

MS(EI) m/e: 316(M⁺), 287, 273, 170, 115, 105, 77.

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Compound (II-a-4)

500MHz ¹H-NMR(DMSO-d₆), δ : 2.67(3H, s), 7.54(1H, t, J=7.3Hz), 7.66(1H, d, J=9.8Hz), 7.70(2H, t, J=7.8Hz), 7.84(1H, dd, J=9.8, 1.0Hz), 8.21(2H, d, J=7.8Hz), 8.24(1H, s), 8.49(1H, d, J=1.0Hz), 10.02(1H, s, -CHO), 12.47
5 (1h, brs).

MS(EI) m/e:330(M⁺), 301, 172, 117, 91, 77.

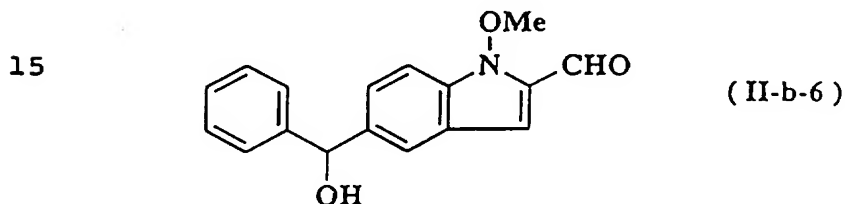
Compound (II-a-5)

60MHz ¹H-NMR(CDCl₃), δ :2.27(3H, s), 4.26(2H, s), 6.42(1H, s), 7.10-8.40
(13H, m), 9.92(1H, s).

10 MS(EI) m/e:456(M⁺), 315, 105, 77.

Synthesis Route 2

Synthesis of 2-formyl-5-(1-hydroxybenzyl)-1-methoxyindole (Compound (II-a-6))



2-formylindole (Compound (II-b)) can be obtained by
20 conducting formylation at the 2-position of 5-bromo-1-methoxyindole synthesized through 5-bromoindoline using 5-bromoindole as a starting material.

1.09 g (5.5598 mmol) of 5-bromoindole was dissolved
in 20 ml of acetic acid, and 2.1 g (33.3 mmol) of sodium
25 cyanoborohydride was added little by little thereto at room temperature. After stirring the resultant mixture at room temperature for 20 minutes, acetic acid was

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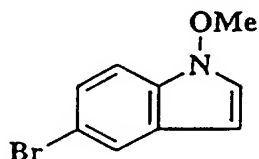
removed by distillation. 40% sodium hydroxide was then added thereto, and the resultant reaction solution was completely neutralized with acetic acid and was extracted with ethyl acetate. After an organic phase obtained was
5 dried with anhydrous sodium sulfate, a residue obtained by removing a solvent by distillation under reduced pressure was subjected to silica gel column chromatography (eluent: ethyl acetate/hexane = 2/1) to obtain 904.2 mg (82.1%) of 5-bromoindoline.

10 Colorless oily material

60MHz ¹H-NMR(CDCl₃), δ : 2.90(2H, brt, J=8.0Hz), 3.42(2H, brt, J=8.0Hz) 3.42(1H, brs), 6.30(1H, d, J=9.0Hz), 6.95(1H, dd, J=9.0, 2.0Hz), 7.01(1H, d, J=2.0Hz).

MS(EI) m/e: 199(M⁺), 197(M⁺), 117, 89.

15 5-bromo-1-methoxyindole (Compound (IX-1))



(IX-1)

20 904.2 mg (4.565 mmol) of 5-bromoindoline was converted by the method disclosed in "Heterocycles" by M. Somei and T. Kawasaki, 1989, 29, 1251 to 739.3 mg (3.2701 mmol, 71.6%) of the subject compound (IX)-1).

Colorless column-like crystals

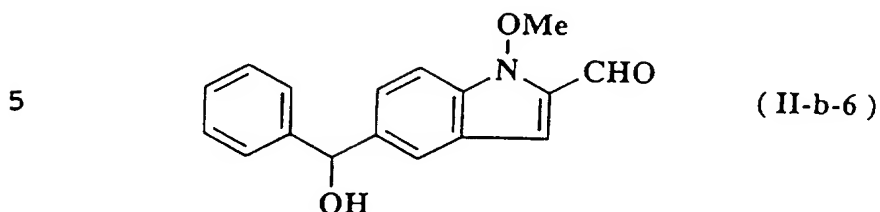
25 Melting point: 44-45°C

500MHz ¹H-NMR(CDCl₃), δ : 4.08(3H, s), 6.29(1H, d, J=3.4Hz), 7.25(1H, d, J=3.4Hz), 7.31(1H, brs), 7.71(1H, brs).

MS(EI) m/e: 227(M⁺), 225(M⁺) 212, 210, 196, 194, 115, 88.

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2-formyl-5-(1-hydroxybenzyl)-1-methoxyindole (Compound (II-b-6))



To an anhydrous tetrahydrofuran (5 ml) solution of 492.9 mg (2.1802 mmol) of Compound (IX-1), was dropwise
10 added 2.35 ml of phenyl lithium (1.02 M solution in ether-cyclohexane, 2.3982 mmol) at -16°C under argon atmosphere. After 15 minutes, 159.4 mg (2.1802 mmol) of anhydrous dimethylformamide was added thereto. After the resultant mixture was stirred at -16°C for 15 minutes as
15 it was, the reaction temperature was lowered to -78°C. After fully lowering the reaction temperature, 2.02 ml of t-butyl lithium (1.61 M solution in pentane, 3.2703mmol) was dropwise added thereto. After 10 minutes, 0.66 ml (6.5406 mmol) of benzaldehyde (Compound (VIII-4)) was
20 added thereto, and the resultant mixture was stirred for 10 minutes. 20 ml of water was added to the resultant reaction mixture, and the reaction mixture was extracted with ethyl acetate to obtain an organic phase. The organic phase thus obtained was washed with a saturated
25 sodium chloride aqueous solution, and the washed organic phase was dried with anhydrous sodium sulfate. Thereafter, the residue obtained by removing a solvent by

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distillation under reduced pressure was subjected to a silica gel column chromatography (eluent: ethyl acetate/hexane = 1/3) to obtain 494.7 mg (80.7%) of the subject compound (II-b-6).

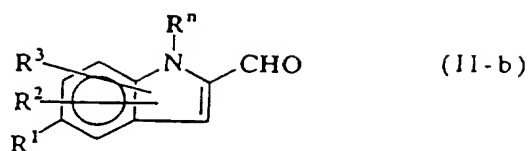
5 Light-yellow oily material

500MHz ¹H-NMR(CDCl₃), δ: 2.32(1H, brs), 4.15(3H, s), 5.95(1H, s), 7.09(1H, d, J=0.7Hz), 7.28(1H, brt, J=8.0Hz), 7.35(2H, brt, J=8.0Hz), 7.41(2H, brd, J=8.0Hz), 7.43(1H, dd, J=9.0, 1.5Hz), 7.46(1H, ddd, J=9.0, 1.5, 0.7Hz), 7.73(1H, dd, J=1.5, 0.7Hz), 9.90(1H, s).

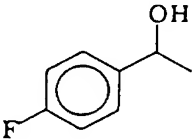
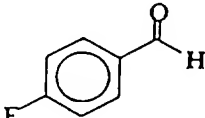
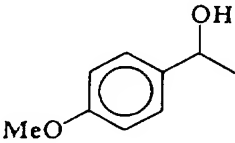
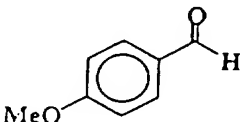
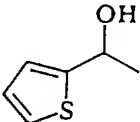
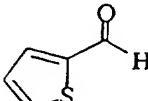
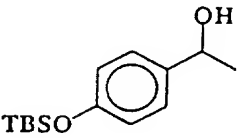
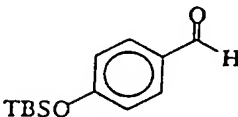
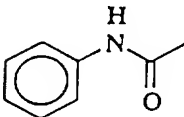
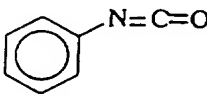
10 MS(EI) m/e: 281(M⁺), 264, 176, 148, 117, 105, 77.

In the same manner as above, electrophilic reagents (Compound (VIII)) were used in place of benzaldehyde to synthesize the following compounds (R¹, R², R³ and Z in the table correspond to the substituent of Compound (II-b)).

15 b)).



| Compound No. | R ¹ | R ² | R ³ | R ⁿ | Electrophile (VIII) | Properties (mp °C) |
|--------------|----------------|----------------|----------------|----------------|---------------------|---|
| II-b-7 | | H | H | MeO | VIII-5 | Yellow oil |
| II-b-8 | | H | H | MeO | VIII-6 | Pale yellow plates (168-168.5) |
| II-b-9 | | H | H | MeO | VIII-3 | Colorless needles (176.5-177.5, decomp.) |
| II-b-10 | | H | H | MeO | VIII-8 | Pale yellow plates (147-148) |
| II-b-11 | | H | H | MeO | VIII-9 | Yellow oil |
| II-b-12 | | H | H | MeO | VIII-10 | Yellow oil |

| Compound No. | R ¹ | R ² | R ³ | R ⁿ | Electrophile (VIII) | Properties (mp °C) |
|--------------|---|----------------|----------------|----------------|---|--------------------------------------|
| II-b-13 |  | H | H | MeO |  VIII-11 | Yellow oil |
| II-b-14 |  | H | H | MeO |  VIII-12 | Yellow oil |
| II-b-15 |  | H | H | MeO |  VIII-13 | Yellow oil |
| II-b-16 |  | H | H | MeO |  VIII-14 | Yellow oil |
| II-b-17 |  | H | H | MeO |  VIII-15 | Pale yellow needles (162.5-163.5) |

Compound (II-b-7)

500MHz $^1\text{H-NMR}(\text{CDCl}_3)$, δ : 2.39(1H, brs), 4.15(3H, s), 6.12(1H, brs), 7.09(1H, s), 7.40-7.52(4H, m), 7.72-7.80(3H, m), 7.94(1H, brs), 9.91(1H, s).
MS(EI) m/e: 331(M^+), 314, 299, 283, 270, 254, 241, 226, 215, 202, 172, 155, 127, 116, 101, 89.

Compound (II-b-8)

500MHz $^1\text{H-NMR}(\text{DMSO-d}_6)$, δ : 4.09(3H, s), 6.10(1H, d, $J=3.9\text{Hz}$), 6.29(1H, d, $J=3.9\text{Hz}$), 7.35(1H, s), 7.51(1H, d, $J=8.0\text{Hz}$), 7.55(1H, d, $J=8.0\text{Hz}$), 7.59(1H, dd, $J=8.0, 8.0\text{Hz}$), 7.71(1H, dd, $J=8.0, 8.0\text{Hz}$), 7.89(1H, s), 7.98(1H, d, $J=9.0\text{Hz}$), 7.99(1H, d, $J=9.0\text{Hz}$), 8.33(1H, brs), 8.90(1H, d, $J=1.0\text{Hz}$), 9.91(1H, s).

MS(EI) m/e: 332(M^+), 315, 255, 245, 202, 156, 128, 117.

Compound (II-b-9)

500MHz $^1\text{H-NMR}(\text{CDCl}_3)$, δ : 2.72(3H, s), 4.24(3H, s), 7.32(1H, s), 7.41(1H, brt, $J=7.6\text{Hz}$), 7.52(2H, brt, $J=7.6\text{Hz}$), 7.63(1H, dd, $J=8.8, 0.7\text{Hz}$), 8.12(2H, brd, $J=7.6\text{Hz}$), 8.39(1H, dd, $J=8.8, 1.5\text{Hz}$), 8.86(1H, dd, $J=1.5, 0.7\text{Hz}$), 9.98(1H, s).

MS(EI) m/e: 360(M^+), 329, 310, 202, 186, 172, 143, 115, 91, 77.

Compound (II-b-10)

500MHz $^1\text{H-NMR}(\text{CDCl}_3)$, δ : 2.86(1H, brs), 4.17(3H, s), 7.04(1H, s), 7.26-7.37(10H, m), 7.45-7.48(2H, m), 7.50-7.52(1H, m), 9.89(1H, s).

MS(EI) m/e: 357(M^+), 280, 249, 220, 202, 183, 165, 143, 116, 105, 89, 77.

Compound (II-b-11)

500MHz $^1\text{H-NMR}(\text{CDCl}_3)$, δ : 2.25(1H, brs), 4.16(3H, s), 5.87(1H, brs), 5.93(1H, d, $J=1.0\text{Hz}$), 5.94(1H, d, $J=1.0\text{Hz}$), 6.78(1H, d, $J=7.8\text{Hz}$), 6.88(1H, d, $J=7.8, 1.0\text{Hz}$), 7.10(1H, s), 7.42(1H, dd, $J=8.6, 1.0\text{Hz}$), 7.47(1H, d, $J=8.6\text{Hz}$), 7.73(1H, d, $J=1.0\text{Hz}$), 9.91(1H, s).

MS(EI) m/e: 325(M^+), 308, 277, 202, 172, 149, 122, 93.

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Compound (II-b-12)

500MHz $^1\text{H-NMR}(\text{CDCl}_3)$, δ : 2.15 (1H, brs), 2.24 (3H, s), 2.32 (3H, s), 4.16 (3H, s), 6.08 (1H, brs), 6.99 (1H, brs), 7.07 (1H, brs), 7.08 (1H, brd, $J=8.3\text{Hz}$), 7.42 (1H, brd, $J=8.3\text{Hz}$), 7.42 (1H, brd, $J=8.3\text{Hz}$), 7.46 (1H, brd, $J=8.3\text{Hz}$), 7.64 (1H, brs), 9.90 (1H, s).

MS(EI) m/e : 309(M^+), 293, 231, 219, 181, 169, 133, 131, 119, 104, 69.

Compound (II-b-13)

500MHz $^1\text{H-NMR}(\text{CDCl}_3)$, δ : 2.30 (1H, brd, $J=3.4\text{Hz}$), 4.16 (3H, s), 5.94 (1H, brd, $J=3.4\text{Hz}$), 7.03 (2H, dd, $J=8.6, 8.6\text{Hz}$), 7.10 (1H, d, $J=0.5\text{Hz}$), 7.37 (2H, dd, $J=10.5, 8.6\text{Hz}$), 7.40 (1H, dd, $J=8.5, 1.5\text{Hz}$), 7.48 (1H, ddd, $J=8.5, 0.7, 0.5\text{Hz}$), 7.71 (1H, dd, $J=1.5, 0.7\text{Hz}$), 9.91 (1H, s).

MS(EI) m/e : 299(M^+), 123.

Compound (II-b-14)

500MHz $^1\text{H-NMR}(\text{CDCl}_3)$, δ : 2.24 (1H, brs), 3.80 (3H, s), 4.16 (3H, s), 5.92 (1H, s), 6.88 (2H, brd, $J=8.8\text{Hz}$), 7.10 (1H, d, $J=0.9\text{Hz}$), 7.31 (2H, brd, $J=8.8\text{Hz}$), 7.42 (1H, dd, $J=8.8, 1.5\text{Hz}$), 7.46 (1H, ddd, $J=8.8, 0.9, 0.9\text{Hz}$), 7.74 (1H, dd, $J=1.5, 0.9\text{Hz}$), 9.91 (1H, s).

MS(EI) m/e : 311(M^+), 294, 263, 202, 135.

Compound (II-b-15)

400MHz $^1\text{H-NMR}(\text{CDCl}_3)$, δ : 2.53 (1H, brs), 4.18 (3H, s), 6.95-7.00 (2H, m), 7.12 (1H, brs), 7.26-7.32 (1H, m), 7.52 (2H, brs), 7.81 (1H, brs), 9.92 (1H, s).

MS(EI) m/e : 287(M^+), 270, 239, 223, 202, 171, 143, 111.

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Compound (II-b-16)

500MHz $^1\text{H-NMR}(\text{CDCl}_3)$, δ : 0.18 (6H, s), 0.97 (9H, s), 2.27 (1H, brs), 4.16 (3H, s), 5.90 (1H, brs), 6.81 (2H, brd, $J=8.5\text{Hz}$), 7.09 (1H, d, $J=0.5\text{Hz}$), 7.23 (2H, brd, $J=8.5\text{Hz}$), 7.42 (1H, dd, $J=8.9, 1.0\text{Hz}$), 7.46 (1H, ddd, $J=8.9, 0.5, 0.5\text{Hz}$), 7.72 (1H, dd, $J=1.0, 0.5\text{Hz}$), 9.90 (1H, s).

MS(EI) m/e : 411(M^+), 354, 323, 305, 294, 266, 235, 201, 150, 135.

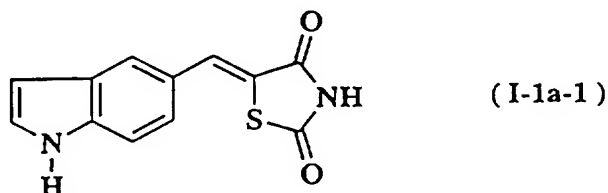
Compound (II-b-17)

400MHz $^1\text{H-NMR}(\text{DMSO}-d_6)$, δ : 4.17 (3H, s), 7.10 (1H, brt, $J=7.5\text{Hz}$), 7.36 (2H, brt, $J=7.5\text{Hz}$), 7.54 (1H, d, $J=0.9\text{Hz}$), 7.73 (1H, dddd, $J=8.8, 1.6, 0.9, 0.7\text{Hz}$), 7.80 (2H, brd, $J=7.5\text{Hz}$), 8.07 (1H, dd, $J=8.8, 1.6\text{Hz}$), 8.49 (1H, dd, $J=1.6, 0.7\text{Hz}$), 9.99 (1H, s), 10.32 (1H, brs).

MS(EI) m/e : 294(M^+), 202, 171, 143, 115, 92, 65.

EXAMPLE 1

Synthesis of 5-(5-indolylmethyldene)thiazolidine-2,4-dione (Compound (I-1a-1)) (Step A)



20

To a toluene (10 ml) solution of 548.7 mg (3.7800 mmol) of Compound (II-1), were added a toluene (0.5 ml) solution of 96.6 mg (1.134 mmol) of piperidine and 885.5 mg (7.56 mmol) of thiazolidine-2,4-dione and a toluene (0.5 ml) solution of 45.4 mg (0.756 mmol) of acetic acid, and the resultant mixture was heat-refluxed for 1 hour. Orange color crystals were precipitated from the reaction

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solution, and the crystals were filtrated and were dissolved in acetone. The solution thus obtained was heated with activated carbon, and methanol was added thereto and a solvent was then removed by distillation
5 under reduced pressure. Crystals precipitated were filtrated and dried to obtain 400.8 mg (43.4%) of the aimed material (compound (I-1a-1)).

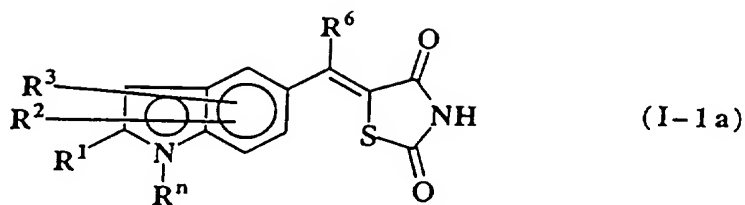
Yellow crystals

Melting point: 320-325°C (dec.) (solvent used for
10 recrystallization: methanol/acetone)

60MHz ¹H-NMR(DMSO-d₆), δ : 6.50(1H, m), 7.21(1H, dd, J=9.0, 2.0Hz), 7.38(1H, d, J=5.0Hz), 7.45(1H, d, J=9.0Hz), 7.75(1H, d, J=2.0Hz), 7.79(1H, s), 11.40(2H, brs).

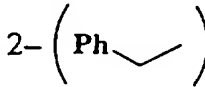
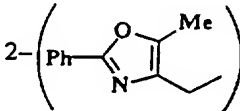
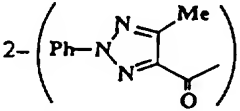
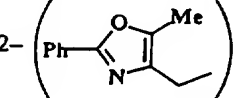
MS(EI) m/e: 244(M⁺), 173, 145, 128.

15 In the same manner as above, the following compounds were synthesized (R¹, R², R³ and Rⁿ and the table correspond to the substituents of Compound (I-1a)).



5

$$(R^4, R^7 = \text{bond}, R^6 = H)$$

| Compound No. | R ¹ | R ² | R ³ | R ⁿ | Starting material (II) | Properties (mp °C) |
|--------------|---|----------------|----------------|--------------------|------------------------|-----------------------------------|
| 10 I-1a-2 | 2-() | H | H | H | II-a-2 | Yellow powder (269-270, decomp.) |
| I-1a-3 | 2-() | H | H | H | II-a-3 | Orange powder (265) |
| 15 I-1a-4 | 2-() | H | H | H | II-a-4 | Yellow powder (315-318, decomp.) |
| I-1a-5 | 2-() | H | H | SO ₂ Ph | II-a-5 | Pale yellow powder (260, decomp.) |

Compound (I-1a-2)

500MHz ¹H-NMR(DMSO-d₆), δ : 4.09(2H, s), 6.28(1H, s), 7.20-7.35(6H, m), 7.41(1H, d, J=8.5Hz), 7.70(1H, d, J=1.0Hz), 7.85(1H, s), 11.38(1H, brs), 12.38(1H, brs).

MS (FAB⁺) m/e: 335 (M⁺), 263, 218.

Compound (I-1a-3)

500MHz ¹H-NMR(DMSO-d₆), δ: 2.73(3H, s), 4.02(2H, s), 6.34(1H, s), 7.27(1H, dd, J=8.5, 1.0Hz), 7.45(1H, d, J=8.5Hz), 7.43-7.55(3H, m), 7.73(1H, d, J=1.0Hz), 7.86(1H, s), 7.92(2H, dd, J=5.8, 1.0Hz), 11.36(1H, brs), 12.43(1H, brs).

MS(EI) m/e: 416 (M⁺), 344, 172.

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Compound (I-1a-4)

500MHz $^1\text{H-NMR}$ (DMSO- d_6), δ : 2.66(3H, s), 7.54(1H, brt, $J=8.0\text{Hz}$), 7.57(1H, d, $J=8.8\text{Hz}$), 7.64(1H, brd, $J=8.8\text{Hz}$), 7.67(2H, brt, $J=8.0\text{Hz}$), 7.87(1H, s), 8.12(1H, s), 8.14(1H, s), 8.21(2H, brd, $J=8.0\text{Hz}$), 12.31(1H, brs), 12.50
5 (1H, brs).

MS(FD) m/e : 429(M^+).

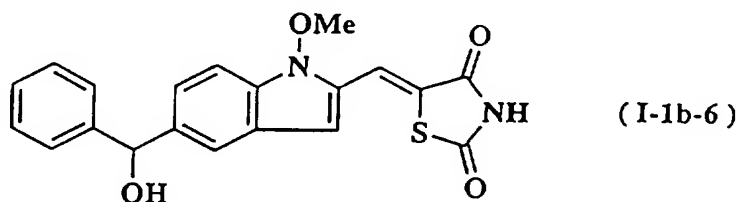
Compound (I-1a-5)

500MHz $^1\text{H-NMR}$ (DMSO- d_6), δ : 2.32(3H, s), 4.29(2H, s), 6.58(1H, s), 7.45-7.65(5H, m), 7.68(1H, t, $J=7.0\text{Hz}$), 7.74(1H, d, $J=1.0\text{Hz}$), 7.82(1H, s), 7.87
10 -8.00(4H, m), 8.18(1H, d, $J=8.8\text{Hz}$), 12.56(1H, brs).

MS(EI) m/e : 555(M^+), 414, 353, 141, 105.

To an ethanol (8 ml) solution of 494.7 mg (1.7586 mmol) of compound (II-b-6), were added 412.0 mg (3.5171 mmol) of thiazolidine-2,4-dione and 29.9 mg (0.3517 mmol) of piperidine. A resultant mixture was heat-refluxed for
15 3 hours, and the reaction solution was cooled. Crystals precipitated were filtrated and dried to obtain 465.9 mg (69.6%) of the aimed compound (I-1b-6).

20



Yellow needle-like crystals

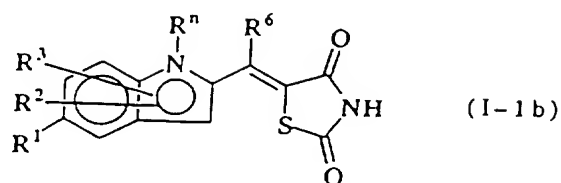
25 Melting point: 222-223°C (dec.) (solvent used for recrystallization: chloroform/ethanol)

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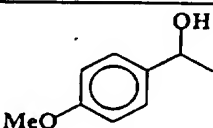
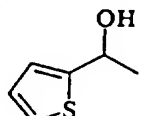
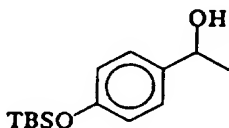
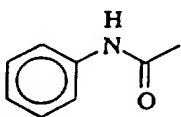
- 500MHz ^1H -NMR(DMSO- d_6), δ : 4.07(3H, s), 5.79(1H, d, $J=3.9\text{Hz}$), 5.89(1H, d, $J=3.9\text{Hz}$), 6.75(1H, s), 7.20(1H, brt, $J=7.5\text{Hz}$), 7.30(2H, brt, $J=7.5\text{Hz}$), 7.33(1H, dd, $J=8.5, 1.0\text{Hz}$), 7.40(2H, brd, $J=7.5\text{Hz}$), 7.48(1H, d, $J=8.5\text{Hz}$), 7.69(1H, s), 7.71(1H, d).
- 5 MS(EI) m/e : 380(M^+), 349, 306, 205, 105.

In the same manner as above, the following compounds were synthesized (R^1 , R^2 , R^6 and R^n correspond to the substituents of Compound (I-1b)).

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(R⁴, R⁷=bond, R⁶=H)

| Compound No. | R ¹ | R ² | R ³ | R ⁿ | Starting material (II) | Properties (mp °C) |
|--------------|----------------|----------------|----------------|----------------|------------------------|------------------------------------|
| I-1b-7 | | H | H | MeO | II-b-7 | Orange powder (226-227) |
| I-1b-8 | | H | H | MeO | II-b-8 | Yellow crystals (260-265, decomp.) |
| I-1b-9 | | H | H | MeO | II-b-9 | Orange powder (260-261, decomp.) |
| I-1b-10 | | H | H | MeO | II-b-10 | Orange amorphous |
| I-1b-11 | | H | H | MeO | II-b-11 | Orange powder (300-350, decomp.) |
| I-1b-12 | | H | H | MeO | II-b-12 | Yellow powder (178-179, decomp.) |
| I-1b-13 | | H | H | MeO | II-b-13 | Yellow needles (224-225, decomp.) |

| Compound No. | R ¹ | R ² | R ³ | R ⁿ | Starting material (II) | Properties (mp °C) |
|---------------|---|----------------|----------------|----------------|------------------------|-----------------------------------|
| 5 I-1b-14 |  | H | H | MeO | II-b-14 | Orange needles (219-220, decomp.) |
| I-1b-15 |  | H | H | MeO | II-b-15 | Orange powder (>224, decomp.) |
| 10 I-1b-16 |  | H | H | MeO | II-b-16 | Yellow needles (111-113) |
| I-1b-17 |  | H | H | MeO | II-b-17 | Yellow powder (200-207, decomp.) |

Compound (I-1b-7)

500MHz ¹H-NMR(DMSO-d₆), δ: 4.06(3H, s), 5.97(1H, d, J=3.0Hz), 6.05(1H, d, J=3.0Hz), 6.76(1H, s), 7.30-8.00(11H, m), 12.65(1H, brs).

MS(EI) m/e: 430(M⁺), 301, 254, 220, 205, 155, 127, 91.

Compound (I-1b-8)

500MHz ¹H-NMR(DMSO-d₆), δ: 4.07(3H, s), 6.08(1H, d, J=3.4Hz), 6.25(1H, d, J=3.4Hz), 7.41(1H, s), 7.38-8.90(10H, m), 12.66(1H, brs).

MS(EI) m/e: 431(M⁺), 400, 357, 330, 301, 255, 216, 200, 172, 156, 128.

Compound (I-1b-9)

500MHz ¹H-NMR(DMSO-d₆), δ: 2.62(3H, s), 4.18(3H, s), 7.07(1H, s), 7.50(1H, brt, J=7.6Hz), 7.63(2H, brt, J=7.6Hz), 7.71(1H, s), 7.74(1H, d, J=8.8Hz), 8.10(2H, brd, J=7.6Hz), 8.18(1H, dd, J=8.8, 1.0Hz), 8.78(1H, d, J=1.0Hz), 12.83(1H, brs).

MS(EI) m/e: 459(M⁺), 385, 357, 225, 199, 171, 143, 127, 91.

Compound (I-1b-10)

500MHz ¹H-NMR(CDCl₃), δ : 3.05 (1H, brs), 4.09 (3H, s), 6.58 (1H, s), 7.20-7.50 (13H, m), 7.91 (1H, s), 8.90 (1H, brs).

MS(EI) m/e: 456(M⁺), 379, 177, 149, 105, 77.

5 Compound (I-1b-11)

500MHz ¹H-NMR(DMSO-d₆), δ : 4.07 (3H, s), 5.71 (1H, d, J=4.0Hz), 5.84 (1H, d, J=4.0Hz), 5.94 (1H, d, J=0.5Hz), 5.95 (1H, d, J=0.5Hz), 6.75 (1H, s), 6.82 (1H, d, J=8.9Hz), 6.87 (1H, dd, J=8.9, 1.0Hz), 6.90 (1H, d, J=1.0Hz), 7.32 (1H, dd, J=8.5, 1.0Hz), 7.47 (1H, d, J=8.5Hz), 7.69 (2H, s), 12.65 (1H, brs).

10

MS(EI) m/e: 424(M⁺), 228, 213, 102.

Compound (I-1b-12)

500MHz ¹H-NMR(DMSO-d₆), δ : 2.16 (3H, s), 2.24 (3H, s), 4.07 (3H, s), 5.69 (1H, d, J=3.8Hz), 5.87 (1H, d, J=3.8Hz), 6.75 (1H, s), 6.91 (1H, brs), 7.01 (1H, brd, J=7.6Hz), 7.26 (1H, dd, J=8.5, 1.0Hz), 7.39 (1H, d, J=7.6Hz), 7.47 (1H, d, J=8.5Hz), 7.58 (1H, brs), 7.69 (1H, s), 12.65 (1H, brs).

15

MS(EI) m/e: 408(M⁺), 379, 358, 275, 205, 172, 133, 105.

Compound (I-1b-13)

500MHz ¹H-NMR(DMSO-d₆), δ : 4.07 (3H, s), 5.80 (1H, d, J=3.8Hz), 5.96 (1H, d, J=3.8Hz), 6.75 (1H, s), 7.12 (2H, t, J=8.3Hz), 7.32 (1H, dd, J=8.6, 1.2Hz), 7.42 (2H, dd, J=8.3, 5.7Hz), 7.48 (1H, d, J=8.6, 0.5Hz), 7.70 (1H, dd, J=1.2, 0.5Hz), 12.65 (1H, brs).

20

MS(FAB⁺) m/e: 398(M⁺).

Compound (I-1b-14)

500MHz ¹H-NMR(DMSO-d₆), δ : 3.38 (3H, s), 4.07 (3H, s), 5.74 (1H, d, J=3.8Hz), 5.80 (1H, d, J=3.8Hz), 6.74 (1H, brs), 6.85 (2H, d, J=8.8Hz), 7.28 (2H, d, J=8.8Hz), 7.31 (1H, dd, J=8.6, 1.0Hz), 7.47 (1H, dd, J=8.6, 0.5Hz), 7.68 (1H, dd, J=1.0, 0.5Hz), 7.69 (1H, s), 12.65 (1H, brs).

25

MS(EI) m/e: 410(M⁺), 220, 205, 172, 135, 108, 77.

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Compound (I-1b-15)

500MHz ¹H-NMR(DMSO-d₆), δ : 4.09 (3H, s), 6.02 (1H, d, J=4.5Hz), 6.23 (1H, d, J=4.5Hz), 6.78 (1H, s), 6.88 (1H, dd, J=4.0, 0.4Hz), 6.92 (1H, dd, J=5.0, 4.0Hz), 7.38 (1H, dd, J=5.0, 0.4Hz), 7.40 (1H, dd, J=8.6, 0.3Hz),
5 7.51 (1H, d, J=8.6Hz), 7.70 (1H, s), 7.75 (1H, d, J=0.3Hz), 12.65 (1H, brs).

MS(EI) m/e: 386(M⁺), 301, 256, 205, 171, 145, 111, 85.

Compound (I-1b-16)

400MHz ¹H-NMR(DMSO-d₆), δ : 0.15 (6H, s), 0.93 (9H, s), 4.07 (3H, s), 5.72
10 (1H, d, J=3.7Hz), 5.82 (1H, d, J=3.7Hz), 6.75 (1H, s), 6.77 (2H, d, J=8.4Hz), 7.25 (2H, d, J=8.4Hz), 7.32 (1H, brd, J=8.3Hz), 7.47 (1H, brd, J=8.3Hz), 7.68 (1H, s), 7.69 (1H, brs), 12.09 (1H, brs).

MS(EI) m/e: 510(M⁺), 422, 378, 205.

Compound (I-1b-17)

15 400MHz ¹H-NMR(DMSO-d₆), δ : 4.17 (3H, s), 6.93 (1H, s), 7.11 (1H, brt, J=7.3Hz), 7.35 (2H, brt, J=7.3Hz), 7.69 (1H, d, J=8.8Hz), 7.72 (1H, s), 7.80 (2H, brd, J=7.3Hz), 7.96 (1H, d, J=8.8Hz), 8.40 (1H, brs), 10.28 (1H, brs), 12.70 (1H, brs).

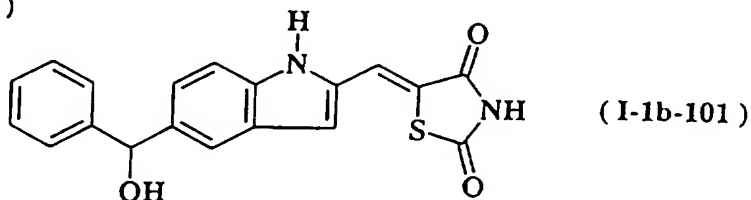
MS(EI) m/e: 393(M⁺), 301, 270, 230, 199, 171, 127, 92, 65.

20 EXAMPLE 2

Removal of substituent Rⁿ (Step C)

Synthesis of 5-((5-(1-hydroxybenzyl)indole-2-yl)methylidene)thiazolidine-2,4-dione (Compound (I-1b-101))

25



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To a tetrahydrofuran-water (12 ml-4 ml) solution of 455.9 mg (1.1984 mmol) of compound (I-1b-6), were added 489.1 mg of magnesium oxide and 476.8 mg of 10% Pd-C, and the resultant mixture was stirred for 20 hours at room temperature under hydrogen atmosphere of 1 atmospheric pressure. After terminating the reaction, the reducing agent was removed by filtration. The solvent in the filtrate was removed by distillation under reduced pressure, and a residue obtained was recrystallized to obtain 409.4 mg (97.5%) of the subject compound (I-1b-101).

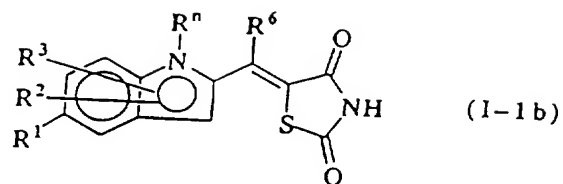
Yellow powder

Melting point: 450°C< (solvent used for recrystallization: THF/benzene)

500MHz ¹H-NMR(DMSO-d₆), δ: 5.77(1H, d, J=3.9Hz), 5.82(1H, d, J=3.9Hz), 6.77(1H, s.), 7.18 (1H, brt, J=9.0Hz), 7.21(1H, d, J=9.0Hz), 7.28(2H, brt, J=9.0Hz), 7.36(1H, d, J=9.0Hz), 7.39(2H, brd, J=9.0Hz), 7.65(1H, s), 7.72(1H, s), 11.59(1H, brs), 12.52(1H, brs).

MS(EI) m/e:350(M⁺), 279, 220, 205, 145, 105, 91, 77.

In the same manner as above, the following compounds were synthesized (R¹, R², R³ and Rⁿ in the table correspond to the substituents of Compound (I-1b)).



(R⁴, R⁷=bond, R⁶=H)

| Compound No. | R ¹ | R ² | R ³ | R ⁿ | Starting material (I-1b) | Properties (mp °C) |
|--------------|----------------|----------------|----------------|----------------|--------------------------|--|
| I-1b-102 | | H | H | H | I-1b-11 | Yellow powder (330-400, decomp.) |
| I-1b-103 | | H | H | H | I-1b-12 | Yellow powder (125-160, decomp.) |
| I-1b-104 | | H | H | H | I-1b-13 | Yellow powder (246-250, decomp.) |
| I-1b-105 | | H | H | H | I-1b-14 | Yellowish orange powder (280-300, decomp.) |
| I-1b-106 | | H | H | H | I-1b-15 | Yellow powder (280-290, decomp.) |

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Compound (I-1b-102)

500MHz ¹H-NMR(DMSO-d₆), δ : 5.68 (1H, d, J=3.9Hz), 5.77 (1H, d, J=3.9Hz),
5.93 (1H, d, J=0.5Hz), 5.95 (1H, d, J=0.5Hz), 6.78 (1H, d, J=1.0Hz), 6.8
1 (1H, d, J=8.0Hz), 6.86 (1H, dd, J=8.0, 1.0Hz), 6.89 (1H, d, J=1.0Hz),
5 7.20 (1H, dd, J=8.6, 1.0Hz), 7.36 (1H, d, J=8.6Hz) 7.63 (1H, d, J=1.0Hz),
7.74 (1H, s), 11.59 (1H, s), 12.50 (1H, brs).

MS(FD⁺) m/e:394(M⁺).

Compound (I-1b-103)

500MHz ¹H-NMR(DMSO-d₆), δ : 2.14 (3H, s), 2.24 (3H, s), 5.62 (1H, d, J=5.0
10 Hz), 5.86 (1H, d, J=5.0Hz), 6.77 (1H, s), 6.90 (1H, s), 7.01 (1H, brd, J
=6.9Hz), 7.14 (1H, brd, J=8.1Hz), 7.36 (1H, d, J=8.1Hz), 7.39 (1H, d, J=
6.9Hz), 7.52 (1H, s), 7.73 (1H, s), 11.59 (1H, brs), 12.50 (1H, brs).

MS(FAB⁺) m/e:379(M⁺+1), 362.

Compound (I-1b-104)

15 500MHz ¹H-NMR(DMSO-d₆), δ : 5.78 (1H, d, J=3.8Hz), 5.89 (1H, d, J=3.8Hz),
6.78 (1H, dd, J=1.0, 0.3Hz), 7.11 (2H, t, J=9.0Hz), 7.20 (1H, dd, J=5.1,
1.0Hz), 7.37 (1H, dd, J=5.1, 0.5, 0.3Hz), 7.40 (2H, dd, J=9.0, 6.1Hz),
7.65 (1H, dd, J=1.0, 0.5Hz), 7.74 (1H, s), 11.61 (1H, brs), 12.52 (1H, brs).

MS(FAB⁺) m/e:368(M⁺+1).

20 Compound (I-1b-105)

500MHz ¹H-NMR(DMSO-d₆), δ : 3.71 (3H, s), 5.71 (1H, d, J=3.8Hz), 5.73 (1H,
d, J=3.8Hz), 6.78 (1H, dd, J=1.0, 0.5Hz), 6.85 (2H, d, J=8.5Hz), 7.19
(1H, dd, J=8.5, 1.0Hz), 7.27 (2H, d, J=8.5Hz), 7.35 (1H, ddd, J=8.5, 0.5,
0.5Hz), 7.63 (1H, dd, J=1.0, 0.5Hz), 7.74 (1H, s), 11.59 (1H, brs), 12.50
25 (1H, brs).

MS(FAB⁺) m/e:381(M⁺+1), 380, 363.

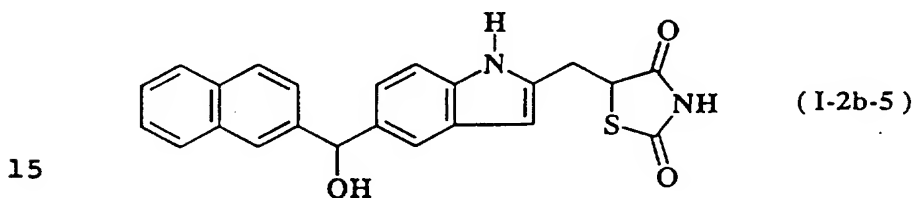
- 208 -

Compound (I-1b-106)

500MHz ¹H-NMR(DMSO-d₆), δ : 5.99 (1H, d, J=4.2Hz), 6.16 (1H, d, J=4.2Hz),
6.81 (1H, dd, J=1.0, 0.5Hz), 6.85 (1H, dd, J=4.0, 1.0Hz), 6.92 (1H, dd,
J=5.1, 4.0Hz), 7.28 (1H, dd, J=8.8, 1.0Hz), 7.37 (1H, dd, J=5.1, 1.0Hz),
5 7.40 (1H, ddd, J=8.8, 0.7, 0.5Hz), 7.69 (1H, dd, J=1.0, 0.5Hz), 7.75 (1
H, s), 11.64 (1H, brs), 12.52 (1H, brs).

MS(EI) m/e: 356(M⁺), 340, 286, 269, 245, 174, 143, 116, 99, 44.

Compound (I-1b-7) was reduced in the same manner as
above, and compound (I-2b-5) wherein the substituent Rⁿ
10 was removed and the connecting part between an indole
ring and a thiazole ring was reduced, was formed.



Light-yellow powder

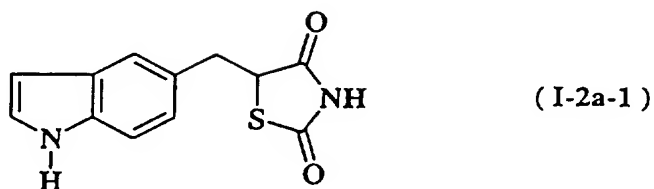
Melting point: 100-108°C (solvent used for
recrystallization: chloroform/hexane)

20 500MHz ¹H-NMR(DMSO-d₆), δ : 3.26(1H, dd, J=15.4, 9.8Hz), 3.50(1H, dd, J=1
5.4, 3.9Hz), 4.94(1H, dd, J=9.8, 3.9Hz), 5.82(1H, d, J=3.9Hz), 5.90(1H,
d, J=3.9Hz), 6.18(1H, s), 7.00-8.00(10H, m), 10.97(1H, s), 12.07(1H, brs).

EXAMPLE 3

Synthesis of 5-(indole-ylmethyl)thiazolidine-2,4-
25 dione (Compound (I-2a-1)) (Step B)

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5

EXAMPLE 3-1 Reduction by hydrogenation

To a tetrahydrofuran (10 ml) solution of 104.7 mg (0.4286 mmol) of compound (I-1a-1), was added 109.7 mg of 10% Pd-C, and the resultant mixture was stirred at room
10 temperature for 20 hours under hydrogen atmosphere of 1 atmospheric pressure. After finishing the reaction, the reducing agent was removed by filtration. The solvent in the filtrate was removed by distillation under reduced pressure, and a residue obtained was dissolved in a
15 solvent of ethyl acetate/hexane (1/1). This solution was filtrated by silica gel, and was subjected to recrystallization to obtain 80.8 mg of the aimed compound (I-2a-1).

Yellow column-like crystals

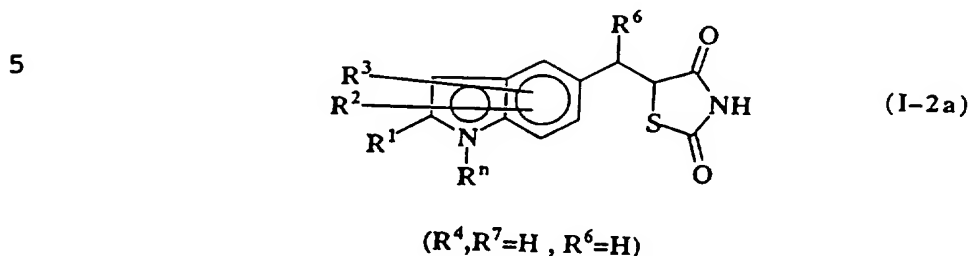
20 Melting point: 159.5-160.5°C (solvent used for recrystallization: ethylacetate/hexane)

60MHz ¹H-NMR(CD₃COCD₃), δ : 3.15(1H, dd, J=12.0, 9.0Hz), 3.60(1H, dd, J=12.0, 5.0Hz), 4.70(1H, dd, J=9.0, 5.0Hz), 6.31(1H, m), 6.90-7.60(4H, m), 10.00(1H, brs).


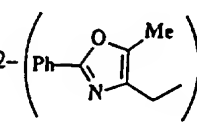
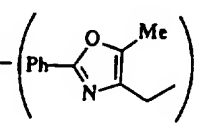
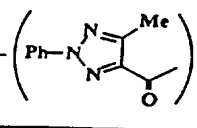
25 MS(EI) m/e: 246(M⁺), 130, 115.

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In the same manner as above, the following compounds were synthesized (R^1 , R^2 , R^3 and R^n in the table correspond to the substituents of Compound (I-2a)).



10

| Compound No. | R^1 | R^2 | R^3 | R^n | Starting material (I-1a) | Properties (mp °C) |
|--------------|--|-------|-------|--------------------|--------------------------|--------------------------------|
| I-2a-2 | 2-(Ph- ) | H | H | H | I-1a-2 | Yellow prisms (132-133) |
| I-2a-3 | 2-(Ph- ) | H | H | H | I-1a-3 | Pale yellow powder (111-112) |
| I-2a-4 | 2-(Ph- ) | H | H | SO ₂ Ph | I-1a-5 | Pale yellow prisms (104-105) |
| I-2a-7 | 2-(Ph- ) | H | H | H | I-1a-4 | Pale yellow crystals (115-116) |

15

20

Compound (I-2a-2)

500MHz ¹H-NMR(CDCl₃), δ : 3.19(1H, dd, J=14.1, 10.1Hz), 3.63(1H, dd, J=14.1, 3.9Hz), 4.13(2H, s), 4.57(1H, dd, J=10.1, 3.9Hz), 6.30(1H, dd, J=1.0, 0.5Hz), 6.97(1H, dd, J=8.3, 1.7Hz), 7.20(1H, ddd, J=8.3, 0.5, 0.5Hz), 7.21-7.27(5H, m), 7.39(1H, dd, J=0.5, 0.5Hz), 7.77 (1H, brs), 7.79 (1H, brs).

MS(FAB⁺) m/e: 337(M⁺), 220.

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Compound (I-2a-3)

500MHz ¹H-NMR(DMSO-d₆), δ : 2.35(3H, s), 3.10(1H, dd, J=7.5, 5.0Hz), 3.42
(1H, dd, J=7.5, 2.5Hz), 3.97(2H, s), 4.88(1H, dd, J=5.0, 2.5Hz), 6.14(1H,
s), 6.89(1H, dd, J=8.0, 1.0Hz), 7.23(1H, d, J=8.0Hz), 7.27(1H, d, J=1.0
5 Hz), 7.45-7.55(3H, m), 7.91(2H, dd, J=8.0, 2.0Hz), 10.90(1H, brs), 11.96
(1H, brs).

MS(FAB⁺) m/e: 418(M⁺), 301, 172.

Compound (I-2a-4)

10 500MHz ¹H-NMR(CDCl₃), δ : 2.30(3H, s), 3.18(1H, dd, J=15.0, 10.0Hz), 3.56
(1H, dd, J=15.0, 5.0Hz), 4.25(2H, s), 4.52(1H, dd, J=10.0, 5.0Hz), 6.31
(1H, s), 7.12(1H, dd, J=8.0, 2.0Hz), 7.30-7.50(6H, m), 7.52(1H, dd, J=8.
0, 8.0Hz), 7.78(2H, dd, J=7.0, 1.0Hz), 7.82(1H, brs), 7.97-8.02(2H, m),
8.11(1H, d, J=8.0Hz).

15 MS(EI) m/e: 557(M⁺), 416, 386, 299.

Compound (I-2a-7)

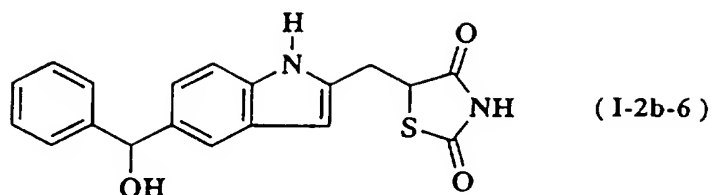
500MHz ¹H-NMR(CDCl₃), δ : 2.65 (3H, s), 3.21 (1H, dd, J=14.2, 8.8Hz), 3.48
(1H, dd, J=14.2, 4.4Hz), 4.95 (1H, dd, J=8.8, 4.4Hz), 7.23 (1H, brd, J=
20 8.5), 7.46 (1H, brd, J=8.5Hz), 7.52 (1H, brt, J=7.6Hz), 7.66 (1H, brs),
7.97 (1H, brs), 8.20 (1H, brt, J=7.6Hz), 11.96 (1H, brs), 12.01 (1H, brs).

MS(EI) m/e: 431(M⁺), 415, 205, 183, 156, 129, 91.

EXAMPLE 3-2 Reduction by amalgam

Synthesis of 5-((5-(1-hydroxybenzyl)indole-2-
25 yl)methyl)thiazolidine-2,4-dione (Compound (I-2a-6))

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5

To a MeOH (3 ml) solution of 119.0 mg (0.3396 mmol) of compound (I-1b-6), was added 3% sodium-amalgam, and the resultant mixture was stirred at room temperature for 18 hours. After finishing the reaction, the reaction mixture was filtrated to remove the reducing agent. The solvent in the filtrate was removed by distillation under reduced pressure, and a residue obtained was subjected to silica gel column chromatography (eluent: tetrahydrofuran/benzene=1/3) to obtain 86.0 mg (61.1%) of the subject compound (I-2b-6).

15

Colorless powder

Melting point: 84-87°C (solvent used for recrystallization: chloroform/hexane)

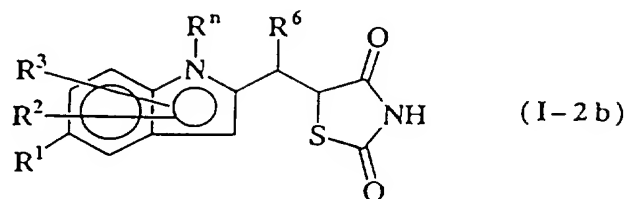
500MHz ¹H-NMR(CDCl₃), δ : 3.42(1H, dd, J=15.4, 7.3Hz), 3.53(1H, dd, J=15.4, 4.9Hz), 4.60(1H, dd, J=7.3, 4.9Hz), 5.95(1H, d, J=2.0Hz), 6.35(1H, d, J=7.8Hz), 7.25(1H, brt, J=7.6Hz), 7.28(1H, d, J=7.6Hz), 7.33(2H, brt, J=7.6Hz), 7.42(2H, brd, J=7.6Hz), 7.56(1H, s), 7.95(1H, brs), 8.26(1H, brs). MS(EI) m/e: 352(M⁺), 236, 205, 105, 78.

20

In the same manner as above, the following compounds were synthesized (R¹, R², R³ and Rⁿ in the table correspond to the substituents of Compound (I-2b)).

25

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(R⁴, R⁷=bond, R⁶=H)

| Compound No. | R ¹ | R ² | R ³ | R ⁿ | Starting material (I-1b) | Properties (mp °C) |
|--------------|----------------|----------------|----------------|----------------|--------------------------|-------------------------------------|
| I-2b-8 | | H | H | H | I-1b-102 | Pale yellow amorphous |
| I-2b-9 | | H | H | H | I-1b-103 | Yellow powder (102-104) |
| I-2b-10 | | H | H | H | I-1b-104 | Pale yellow powder (77-81) |
| I-2b-11 | | H | H | H | I-1b-105 | Pale yellow powder (75-77, decomp.) |
| I-2b-12 | | H | H | H | I-1b-106 | Pale yellow powder (68-69, decomp.) |

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Compound (I-2b-8)

500MHz ¹H-NMR(DMSO-d₆), δ : 3.25 (1H, dd, J=15.2, 10.0Hz), 3.51 (1H, dd, J=15.2, 3.6Hz), 4.94 (1H, dd, J=10.0, 3.6Hz), 5.63 (1H, d, J=4.5Hz), 5.64 (1H, d, J=4.5Hz), 5.92 (1H, brs), 5.93 (1H, brs), 6.18 (1H, brs), 6.79 (1H, d, J=8.0Hz), 6.83 (1H, dd, J=8.0, 1.0Hz), 6.88 (1H, d, J=1.0Hz), 7.01 (1H, brd, J=8.5Hz), 7.20 (1H, brd, J=8.5Hz), 7.41 (1H, brs), 10.96 (1H, brs), 12.07 (1H, brs).

MS(EI) m/e: 396(M⁺+1), 280, 149.

Compound (I-2b-9)

500MHz ¹H-NMR(DMSO-d₆), δ : 2.12 (3H, s), 2.23 (3H, s), 3.24 (1H, dd, J=17.5, 9.5Hz), 3.51 (1H, dd, J=17.5, 5.0Hz), 4.95 (1H, dd, J=9.5, 5.0Hz), 5.46 (1H, d, J=4.5Hz), 5.81 (1H, d, J=4.5Hz), 6.16 (1H, brs), 6.88 (1H, brs), 6.95 (1H, brd, J=8.0Hz), 6.99 (1H, brd, J=8.0Hz), 7.20 (1H, brd, J=8.0Hz), 7.31 (1H, brs), 7.41 (1H, brd, J=8.0Hz), 10.97 (1H, brs), 12.09 (1H, brs).

MS(FAB⁺) m/e: 381(M⁺+1), 364.

Compound (I-2b-10)

500MHz ¹H-NMR(DMSO-d₆), δ : 3.27 (1H, dd, J=15.4, 9.8Hz), 3.51 (1H, dd, J=15.4, 4.2Hz), 4.95 (1H, dd, J=9.8, 4.2Hz), 5.73 (1H, d, J=3.9Hz), 5.75 (1H, d, J=3.9Hz), 6.18 (1H, brs), 7.00 (1H, brd, J=8.3Hz), 7.08 (2H, J=8.8Hz), 7.21 (1H, brd, J=8.3Hz), 7.39 (2H, dd, J=8.8, 5.8Hz), 7.42 (1H, brs), 10.89 (1H, brs), 12.09 (1H, brs).

MS(FAB⁺) m/e: 371(M⁺+1), 370, 353, 307, 254.

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Compound (I-2b-11)

500MHz ¹H-NMR(DMSO-d₆), δ : 3.70 (3H, s), 5.58 (1H, d, J=3.9Hz), 5.67 (1H, d, J=3.9Hz), 6.17 (1H, brs), 6.83 (2H, d, J=9.5Hz), 7.00 (1H, brd, J=4.3Hz), 7.20 (1H, brd, J=4.3Hz), 7.26 (2H, d, J=9.5Hz), 7.40 (1H, brs), 10.96 (1H, brs), 12.07 (1H, brs).

MS(FAB⁺) m/e: 382(M⁺), 365, 266, 249, 135, 119.

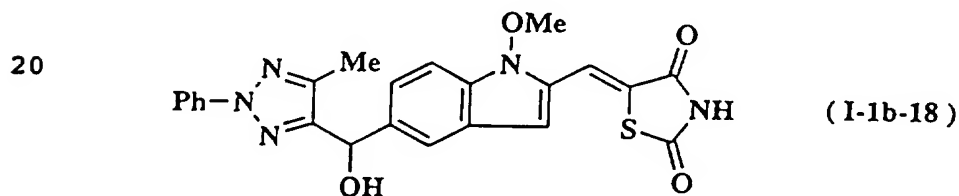
Compound (I-2b-12)

500MHz ¹H-NMR(DMSO-d₆), δ : 3.27 (1H, dd, J=15.0, 10.0Hz), 3.52 (1H, dd, J=15.0, 3.9Hz), 4.96 (1H, dd, J=10.0, 3.9Hz), 5.94 (1H, d, J=4.2Hz), 6.02 (1H, d, J=4.2Hz), 6.20 (1H, brs), 6.82 (1H, dd, J=3.4, 1.2Hz), 6.90 (1H, dd, J=5.3, 3.4Hz), 7.09 (1H, brd, J=8.3Hz), 7.25 (1H, brd, J=8.3Hz), 7.33 (1H, dd, J=5.3, 1.2Hz), 7.48 (1H, brs), 11.03 (1H, brs), 12.10 (1H, brs).

MS(FAB⁺) m/e: 358(M⁺), 341, 242.

15 EXAMPLE 4

Synthesis of 5-((1-methoxy-5-hydroxy(2-phenyl-5-methyl-1,2,3-triazol-4-yl)methylindol-2-yl)methylidenethiazolidine-2,4-dione (Compound (I-1b-18))



To a tetrahydrofuran (5 ml) solution of 129.8 mg (0.2825 mmol) of compound (I-1b-9), was added 21.4 mg (0.5650 mmol) of sodium borohydride at room temperature, and the resultant mixture was stirred for 1 hour. After finishing the reaction, water and 2M hydrochloric acid

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were added to the reaction solution and the reaction solution was extracted with a mixed solvent of chloroform: MeOH=9:1. An organic phase obtained was washed with a saturated sodium chloride aqueous solution,
5 and a solvent was removed by distillation under reduced pressure. A residue obtained was recrystallized from chloroform/hexane to obtain 127.9 mg (98.1%) of Compound (I-1b-18).

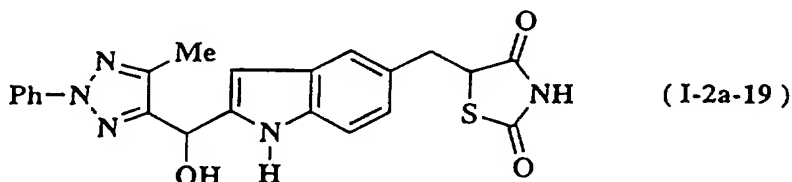
Orange crystals

10 Melting point: 170-176°C (decomposition) (solvent used for recrystallization: chloroform/hexane)

500MHz ¹H-NMR(DMSO-d₆), δ :2.21 (3H, s), 4.07 (3H, s), 6.08 (1H, d, J=4.3 Hz), 6.19 (1H, d, J=4.3Hz), 6.79 (1H, s), 7.35 (1H, brt, J=7.5Hz), 7.40 (1H, d, J=8.0Hz), 7.53 (2H, brt, J=7.5Hz), 7.45 (1H, d, J=8.0Hz), 7.68
15 (1H, s), 7.27 (1H, brs), 7.93 (2H, brt, J=7.5Hz), 12.63 (1H, brs).
MS(EI) m/e:461(M⁺), 431, 387, 362, 331, 301, 186, 172, 117.

EXAMPLE 5

Synthesis of 5-((2-hydroxy(2-phenyl-5-methyl-1,2,3-tiazol-4-yl)methylindol-5-yl)methyl)thiazolidine-2,4-
20 dione (Compound (I-2a-19))



25

To a tetrahydrofuran (3 ml) solution of 100.5 mg (0.2329 mmol) of Compound (I-2a-7), was added 26.4 mg

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(0.6988 mmol) of sodium borohydride at room temperature, and the resultant mixture was stirred for 3 hours. After finishing the reaction, water and 2M hydrochloric acid were added to the reaction solution and the reaction solution was extracted with a mixed solvent of chloroform: MeOH=9:1. An organic layer obtained was washed with a saturated sodium chloride aqueous solution, and a solvent was removed by filtration under reduced pressure. A residue obtained was recrystallized with chloroform-hexane, and the recrystallized material was subjected to silica gel column chromatography (eluent: tetrahydrofuran/hexane = 1/2) and was further recrystallized from chloroform-hexane to obtain 14.8 mg (14.7%) of Compound (I-2a-19).

Colorless crystals

Melting point: 103-108°C(decomposition) (solvent used for recrystallization: chloroform/hexane)

500MHz ¹H-NMR(DMSO-d₆), δ :3.10 (1H, dd, J=14.0, 9.8Hz), 3.44 (1H, dd, J=14.1, 4.2Hz), 4.89 (1H, dd, J=9.8, 4.2Hz), 6.13 (1H, d, J=4.6Hz), 6.22 (1H, brs), 6.28 (1H, d, J=4.6Hz), 6.93 (1H, brd, J=8.3Hz), 7.28 (1H, brd, J=8.3Hz), 7.32 (1H, brs), 7.73 (1H, brt, J=7.8Hz), 7.53 (2H, brt, J=7.8 Hz), 7.95 (2H, brd, J=7.8Hz), 11.05 (1H, brs), 11.97 (1H, brs).

MS(EI) m/e:433(M⁺), 315, 299, 187, 158, 130.

20 mg (0.0479 mmol) of Compound (I-2a-3) was dissolved in 2 ml of a methanol/tetrahydrofuran mixture solution (1/1 v/v). 2.57 ml of sodium hydroxide aqueous solution (74.7 mg%) was added to the above prepared

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solution of Compound (I-2a-3), and the resultant mixture was stirred at room temperature for 1 hour and 20 minutes. Thereafter, a solvent was removed by distillation under reduced pressure and an aqueous solution of a residue obtained was freeze-dried to obtain 16.4 mg (77.9%) of Compound (I-4a-1).

Colorless crystals

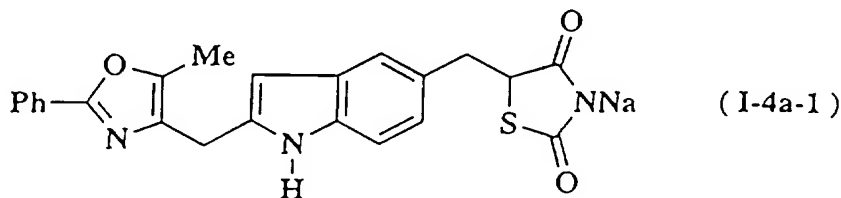
Melting point: 260-265°C (decomposition)

MS(FAB⁺) m/e: 439(M⁺)

10 EXAMPLE 6

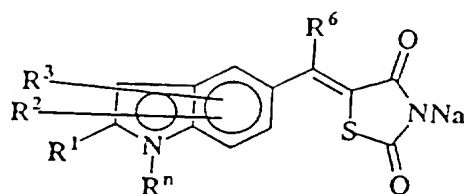
Preparation of sodium salt of 5-(((2-phenyl-5-methyl-1,2,3-triazol-4-yl)methyl)indol-5-yl)methyl)thiazolidine-2,4-dione (Compound (I-4a-1))

15



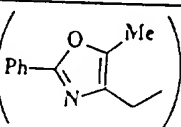
In the same manner as above, the following compounds were synthesized (R¹, R², R³ and Rⁿ in the table correspond to the substituents of Compounds (I-3a, I-4a, I-3b and I-4b)).

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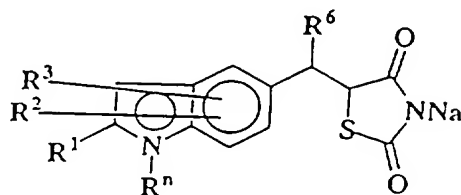


(I-3a)

(R⁴, R⁷=H, R⁶=H)

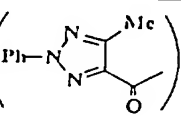
| Compound No. | R ¹ | R ² | R ³ | R ⁿ | Starting materials (I-1a) | Properties (mp °C) |
|--------------|--|----------------|----------------|--------------------|---------------------------|--|
| I-3a-1 | 2-(Ph- ) | H | H | SO ₂ Ph | I-1a-5 | Colorless amorphous (160-180, decomp.) |

Compound (I-3a-1)

MS(FAB⁺) m/e: 578 (M⁺+1).

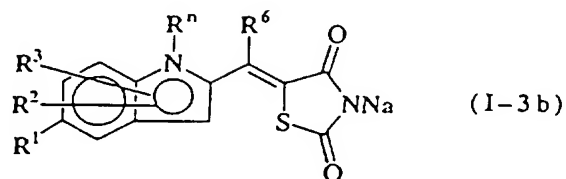
(I-4a)

(R⁴, R⁷=H, R⁶=H)

| Compound No. | R ¹ | R ² | R ³ | R ⁿ | Starting materials (I-2a) | Properties (mp °C) |
|--------------|--|----------------|----------------|----------------|---------------------------|----------------------------------|
| I-4a-2 | 2-(Ph- ) | H | H | H | I-2a-7 | Yellow powder (180-250, decomp.) |

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Compound (I-4a-2)

MS(FD) m/e: 476 ($M^+ + Na$), 454 ($M^+ + 1$), 431 ($M^+ - Na + 1$).

(I-3b)

(R⁴, R⁷=bond, R⁶=H)

| Compound No. | R ¹ | R ² | R ³ | R ⁿ | Starting materials (I-1b) | Properties (mp °C) |
|--------------|----------------|----------------|----------------|----------------|---------------------------|-------------------------------------|
| I-3b-2 | | H | H | MeO | I-1b-6 | Yellow amorphous (220-230, decomp.) |
| I-3b-3 | | H | H | MeO | I-1b-7 | Yellow amorphous (260-280, decomp.) |
| I-3b-4 | | H | H | MeO | I-1b-8 | Yellow amorphous (195-230, decomp.) |
| I-3b-5 | | H | H | MeO | I-1b-11 | Yellow amorphous (180-230, decomp.) |
| I-3b-6 | | H | H | MeO | I-1b-13 | Yellow amorphous (172-176, decomp.) |
| I-3b-7 | | H | H | MeO | I-1b-14 | Yellow amorphous (164-170, decomp.) |
| I-3b-8 | | H | H | MeO | I-1b-15 | Yellow amorphous (240-260, decomp.) |

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Compound (I-3a-2)

MS(FAB⁺) m/e:403(M⁺+1).

Compound (I-3a-3)

MS(FAB⁺) m/e:403(M⁺+1).

5 Compound (I-3a-5)

MS(FD) m/e:424(M⁺-Na+1).

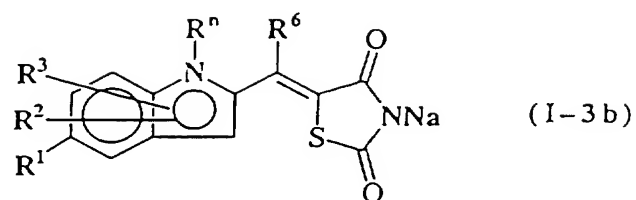
Compound (I-3a-7)

MS(FD) m/e:410(M⁺-Na+1).

Compound (I-3a-8)

10 MS(FAB⁺) m/e:387(M⁺-Na+1), 386.

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(R⁴, R⁷=bond, R⁶=H)

| Compound No. | R ¹ | R ² | R ³ | R ⁿ | Starting materials (I-1b) | Properties (mp °C) |
|--------------|----------------|----------------|----------------|----------------|---------------------------|--|
| I-3b-9 | | H | H | H | I-1b-101 | Yellow crystals (220-400, decomp.) |
| I-3b-10 | | H | H | H | I-1b-102 | Yellow crystals (200-400, decomp.) |
| I-3b-11 | | H | H | H | I-1b-103 | Yellow amorphous (190-210, decomp.) |
| I-3b-12 | | H | H | H | I-1b-104 | Colorless amorphous (190-220, decomp.) |

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Compound (I-3b-9)

MS(FAB⁺) m/e:395(M⁺+Na), 373.

Compound (I-3b-10)

MS(FAB⁺) m/e:439(M⁺+Na), 417, 416.

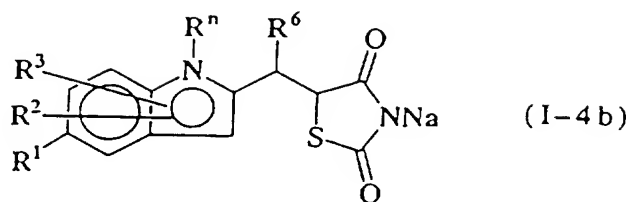
5 Compound (I-3b-11)

MS(FAB⁺) m/e:423(M⁺+Na), 401(M⁺+1), 400(M⁺).

Compound (I-3b-12)

MS(FAB⁺) m/e:412(M⁺+Na-1), 390(M⁺).

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(R⁴, R⁷=bond, R⁶=H)

| Compound No. | R ¹ | R ² | R ³ | R ⁿ | Starting materials (I-2b) | Properties (mp °C) |
|--------------|----------------|----------------|----------------|----------------|---------------------------|--|
| I-4b-3 | | H | H | H | I-2b-5 | Pale brown crystals (180-300, decomp.) |
| I-4b-4 | | H | H | H | I-2b-8 | Pale red amorphous (200-300, decomp.) |
| I-4b-5 | | H | H | H | I-2b-9 | Yellow amorphous (210-290, decomp.) |
| I-4b-6 | | H | H | H | I-2b-10 | Colorless amorphous |

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Compound (I-4b-3)

MS(FD) m/e:447(M^+ +Na), 425(M^+ +1).

Compound (I-4b-4)

MS(FD) m/e:441(M^+ +Na), 419(M^+ +1).

5 Compound (I-4b-5)

MS(FD) m/e:425(M^+ +Na), 403(M^+ +1).

Compound (I-4b-6)

MS(FAB⁺) m/e:414(M^+ +Na).

TEST EXAMPLE 1: Measurement of hypoglycemic effect

10 KK mouse and KKA^y mouse, NIDDM models (male, 6-7 weeks old) (Nakamura, Proc. Jpn. Acad., vol. 38, 348-352, 1962; Iwatsuka et al. Endocrinol. Jpn., vol. 17, 23-35, 1970) were purchased from Nihon Clea. They were allowed free access to high-calories' chow (CMF, Oriental Yeast)
15 and water. Around 40 g-weighted mice were examined.

Blood (20 μ l) collected from the retro-orbital sinus was diluted in 60 units heparin sodium-solution and was centrifuged in a microfuge. The supernatant was assayed. The glucose concentration was determined by glucose
20 oxidase method (Glucose Analyzer II, Beckman). A group of 3 to 4 mice having a blood glucose value of higher than 200 mg/dl, the blood glucose value of which did not reduce by more than 10% for 24 hours after once oral administration of 0.5% carboxymethyl cellulose (CMC)-
25 saline, were tested.

All test-compounds suspended in 0.5% carboxy-methyl cellulose (CMC)-saline were orally administered in mice.

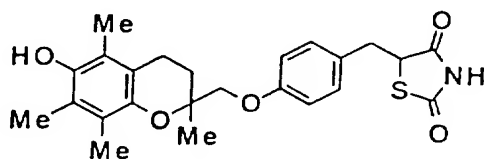
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Before and 24 hours after the administration, blood was collected from the retro-orbital sinus, and a blood glucose value was measured in the above-mentioned manner. The hypoglycemic activity was expressed by the percentage
5 of reducing blood glucose calculated before and 24 hours after the administration.

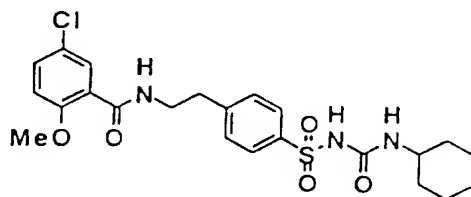
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KKA^y mouse

| Compound No. | Dose (mg/kg) | % decrease |
|---------------|--------------|------------|
| I-1a-1 | 30 | 17.6 |
| I-1a-3 | 30 | 23.4 |
| I-1a-4 | 30 | 26.5 |
| I-1b-7 | 30 | 14.2 |
| I-1b-13 | 30 | 12.7 |
| I-1b-14 | 30 | 23.8 |
| I-1b-17 | 30 | 17.5 |
| I-1b-18 | 30 | 22.6 |
| I-1b-103 | 30 | 14.1 |
| I-1b-105 | 30 | 19.6 |
| I-2a-1 | 30 | 16.0 |
| I-2a-2 | 30 | 27.9 |
| I-2a-4 | 30 | 15.1 |
| I-2b-6 | 30 | 38.0 |
| I-2b-8 | 30 | 10.8 |
| I-2b-10 | 30 | 20.9 |
| I-2a-19 | 30 | 32.2 |
| I-3b-5 | 30 | 25.0 |
| I-3b-8 | 30 | 18.8 |
| I-3b-9 | 30 | 17.5 |
| I-3b-12 | 30 | 17.0 |
| I-4a-1 | 30 | 28.0 |
| I-4b-5 | 30 | 28.4 |
| CS-045 | 30 | -3.0 |
| Glibenclamide | 30 | -2.5 |



CS-045



Glibenclamide

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The compounds of the present invention exhibited hypoglycemic activities at substantially higher degree as compared with CS-045 used as controls. Glibenclamide (insulin-releasing agent) did not exhibit hypoglycemic activity in this test.

TEXT EXAMPLE 2: Measurement of hypoglycemic and hypolipidemic effect

db/db mice, NIDDM model (male 6 weeks old), were purchased from Nihon Charles River. They were allowed free access to chow (MF, Oriental Yeast) and water. Around 50 g-weighted mice were examined.

Blood (20 μ l) collected from the retro-orbital sinus was diluted in 60 units heparin sodium-solution and was centrifuged in a microfuge. The supernatant was assayed. The glucose concentration was determined by glucose oxidase method (Glucose Analyzer II, Beckman). A group of 6 mice were tested.

All test-compounds suspended in 0.5% carboxy-methyl cellulose (CMC)-saline were orally administered in mice once a day for 4 days. Before, 1 day, 2 days, 3 days and 4 days after the administration, blood was collected from the retro-orbital sinus, and a blood glucose value was measured in the above-mentioned manner. The hypoglycemic activity was expressed by the percentage of reducing blood glucose calculated before and 1 day, 2 days, 3 days or 4 days after the administration.

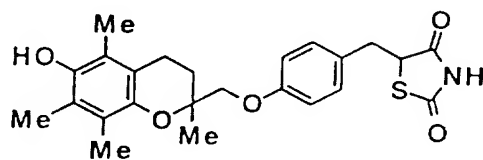
The total cholesterol (TC) amounts in bloods

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collected before drug-administration and 4 days after the drug-administration were measured in accordance with the cholesterol oxidase method and the triglyceride (TG) amounts in these bloods were measured by the end point method employing glycerol oxidase method. The neutral lipid reducing activity in each blood was expressed by a reducing rate relative to the value before the drug-administration.

The compounds of the present invention exhibited higher hypoglycemic activities and higher neutral lipid reducing activities as compared with CS-045 used as controls.

| Compound No. | Dose (mg/kg) | % decrease of glucose | % decrease of TC | % decrease of TG |
|--------------|-----------------|--------------------------|---------------------|---------------------|
| I-2b-6 | 30 | 10.5 | 19.5 | 13.8 |
| CS-045 | 300 | 17.7 | 7.1 | 36.9 |



CS - 0 4 5

TEST EXAMPLE 3: Measurement of aldose-reductase
inhibitory activities

Rat kidney AR was prepared as follows; Rat kidney was

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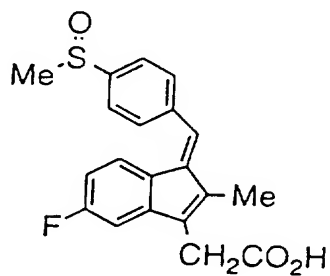
perfused by ice-cold saline to remove blood and then homogenized in a Teflon homogenizer with 3 time volumes of cold 5 mM Tris-HCl buffer (pH 7.4). The homogenate was centrifuged at 45,000 x g for 40 minutes to remove insoluble materials, and the supernatant fraction was dialyzed overnight against 0.05 M sodium chloride solution. The dialyzed solution was centrifuged again at 11,000 x g for 20 minutes and the supernatant fraction was used as an aldose reductase sample.

10 Determination of AR and effects of test compounds

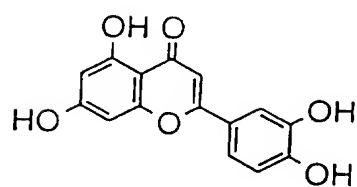
AR activity was assayed by the modified method of Inukai et al. (Jpn. J. Pharmacol. 61, 221-227, 1993). The absorbance of NADPH (340 nm), oxidation of the co-factor for AR, was determined by spectrophotometer (UV-240, Shimadzu, Kyoto). The assay was carried out in 0.1M sodium phosphate (pH 6.2) containing 0.4M lithium sulfate, 0.15 mM NADPH, the enzyme, various concentrations of test compounds and 10 mM DL-glyceraldehyde. The reference blank contained all of the above ingredients, except for DL-glyceraldehyde. The reaction was started by addition of the substrate (DL-glyceraldehyde). The reaction rate was measured at 30°C for 2 minutes. All test compounds were dissolved in dimethyl sulfoxide (DMSO). The final concentration of DMSO in reaction mixture never exceeded 1%.

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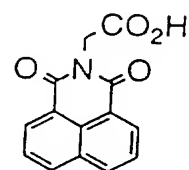
| Compound No. | Concentration(μ M) | % inhibition |
|--------------|-------------------------|--------------|
| I-1a-4 | 30 | 100.0 |
| I-1b-14 | 30 | 53.4 |
| I-2b-6 | 100 | 36.3 |
| I-2b-10 | 30 | 23.3 |
| I-3b-5 | 30 | 49.6 |
| CS-045 | 100 | 0 |
| Sulindac | 30 | 54.0 |
| Quercetin | 30 | 10.8 |
| Alrestatin | 100 | 0 |



Sulindac



Quercetin



Alrestatin

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The compounds of the present invention exhibited equivalent or stronger aldose-reductase inhibitory activities than sulindac, quercetin or alrestatin used as control. Further, CS-045 exhibited no activities.

5 FORMULATION EXAMPLE 1

Tablets

| | | |
|-------|---------------------------------------|--------|
| | The compound of the present invention | 1.0 g |
| | Lactose | 5.0 g |
| | Crystal cellulose powder | 8.0 g |
| 10 | Corn starch | 3.0 g |
| | Hydroxypropyl cellulose | 1.0 g |
| | CMC-Ca | 1.5 g |
| | Magnesium stearate | 0.5 g |
| <hr/> | | |
| 15 | Total | 20.0 g |

The above components were mixed by a usual method and then tabletted to produce 100 tablets each containing 10 mg of the active ingredient.

20 FORMULATION EXAMPLE 2

Capsules

| | | |
|-------|---------------------------------------|--------|
| | The compound of the present invention | 1.0 g |
| | Lactose | 3.5 g |
| | Crystal cellulose powder | 10.0 g |
| 25 | Magnesium stearate | 0.5 g |
| <hr/> | | |
| | Total | 15.0 g |

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The above components were mixed by a usual method and then packed in No. 4 gelatin capsules to obtain 100 capsules each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 3

5 Soft capsules

| | | |
|-------|---------------------------------------|---------|
| | The compound of the present invention | 1.00 g |
| | PEG (polyethylene glycol) 400 | 3.89 g |
| | Saturated fatty acid triglyceride | 15.00 g |
| | Peppermint oil | 0.01 g |
| 10 | Polysorbate 80 | 0.10 g |
| <hr/> | | |
| | Total | 20.00 g |

The above compounds were mixed and packed in No. 3
15 soft gelatin capsules by a usual method to obtain 100 soft capsules each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 4

Ointment

| | | |
|-------|---------------------------------------|-----------------|
| 20 | The compound of the present invention | 1.0 g (10.0 g) |
| | Liquid paraffin | 10.0 g (10.0 g) |
| | Cetanol | 20.0 g (20.0 g) |
| | White vaseline | 68.4 g (59.4 g) |
| | Ethylparaben | 0.1 g (0.1 g) |
| 25 | <i>l</i> -menthol | 0.5 g (0.5 g) |
| <hr/> | | |
| | Total | 100.0 g |

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The above components were mixed by a usual method to obtain a 1% (10%) ointment.

FORMULATION EXAMPLE 5

Suppository

| | | |
|-------|--|---------|
| 5 | The compound of the present invention | 1.0 g |
| | Witepsol H15* | 46.9 g |
| | Witepsol W35* | 52.0 g |
| | Polysorbate 80 | 0.1 g |
| <hr/> | | |
| 10 | Total | 100.0 g |
| | *: Trademark for triglyceride compound | |

The above components were melt-mixed by a usual method and poured into suppository containers, followed
15 by cooling for solidification to obtain 100 suppositories of 1 g each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 6

Granules

| | | |
|----|---------------------------------------|--------|
| | The compound of the present invention | 1.0 g |
| 20 | Lactose | 6.0 g |
| | Crystal cellulose powder | 6.5 g |
| | Corn starch | 5.0 g |
| | Hydroxypropyl cellulose | 1.0 g |
| | Magnesium stearate | 0.5 g |
| 25 | <hr/> | |
| | Total | 20.0 g |

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The above components were granulated by a usual method and packaged to obtain 100 packages each containing 200 mg of the granules so that each package contains 10 mg of the active ingredient.

5

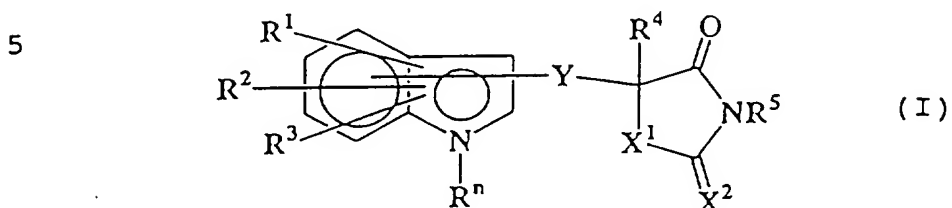
INDUSTRIAL APPLICABILITY

Since the compound of the present invention has a hypoglycemic effect and an aldose-reductase inhibitory activity and has less toxicity, it is useful for preventing or treating diabetic complications including
10 diabetic eye diseases (such as diabetic cataract and diabetic retinopathy), diabetic neuropathy, diabetic nephropathy, diabetic gangrene, and the like.

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CLAIMS

1. An indole type thiazolidine compound of the following formula (I) and its salt:



wherein X^1 is S or O;

10 X^2 is S, O or NH;

Y is CR^6R^7 (R^6 is a hydrogen atom, a C_1 - C_7 alkyl group or a C_3 - C_7 cycloalkyl group, and R^7 is a hydrogen atom, a C_1 - C_7 alkyl group or a C_3 - C_7 cycloalkyl group, or forms a bond together with R^4);

15 R^1 is a substituent at the 2-, 3-, 4-, 5-, 6- or 7-position of an indole ring and is a C_1 - C_{10} alkyl group, a C_2 - C_{10} alkenyl group, a C_2 - C_{10} alkynyl group, a C_1 - C_{10} alkoxy group, a C_2 - C_{10} alkenyloxy group, a C_1 - C_{10} alkylthio group, a C_1 - C_{10} monoalkylamino group or a di-
 20 C_1 - C_{10} alkylamino group (each of said C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_1 - C_{10} alkoxy, C_2 - C_{10} alkenyloxy, C_1 - C_{10} alkylthio, C_1 - C_{10} monoalkylamino and di- C_1 - C_{10} alkylamino groups may be substituted with a hydroxyl group or a C_1 - C_7 alkyl group), or

25 $-W_k-V_l-Z$ (Z is a C_3 - C_{10} cycloalkyl group, a C_3 - C_7 cycloalkenyl group, a C_6 - C_{14} aromatic group, a C_1 - C_{12} heterocyclic aromatic group (said heterocyclic aromatic

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group may contain at most 5 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom as constituents for the heterocyclic ring), or a C₁-C₆ heterocycloaliphatic group (said

5 heterocycloaliphatic group may contain at most 3 hetero atoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom as constituents for the heterocyclic ring) (each of said C₃-C₁₀ cycloalkyl, C₃-C₇ cycloalkenyl, C₆-C₁₄ aromatic, C₁-C₁₂

10 heterocyclic aromatic and C₁-C₆ heterocycloaliphatic groups may have at most 5 substituents selected from the group consisting of a hydrogen atom, a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group, a C₃-C₇ cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be

15 substituted with a hydroxyl group), a hydroxyl group, a C₁-C₇ alkoxy group, a C₁-C₇ alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl

20 group, a C₁-C₃ alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C₁-C₇-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl,

25 thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C₁-C₇ alkyl group, a C₃-C₇

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cycloalkyl group, a C₁-C₃ alkoxy group, a C₁-C₃ alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a
5 thiazolidindion-5-yl group and a thiazolidindion-5-yl methyl group),

V is O, S, SO, SO₂ or NR⁸ (R⁸ is a hydrogen atom or a C₁-C₃ alkyl group),

W is a divalent C₁-C₆ saturated or C₂-C₆ unsaturated
10 hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C₁-C₇ alkyl groups, and

each of k and ℓ is 0 or 1),

-V-W-Z (V, W and Z are as defined above), or

-W-V-W-Z (V, W and Z are as defined above, and two
15 W's may be the same or different), or

R¹ may be a hydrogen atom when Y is bonded to the 4-, 5-, 6- or 7-position of an indole ring;

each of R² and R³ is a substituent at the 2-, 3-, 4-, 5-, 6- or 7-position of an indole ring, and is
20 independently a hydrogen atom, a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group (said C₁-C₇ alkyl and C₃-C₇ cycloalkyl groups may be substituted with a hydroxyl group), a C₁-C₇ alkoxy group, a benzyloxy group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group, a
25 pyrimidinyl group, a pyridazinyl group, a furanyl group, a thienyl group, a pyrrolyl group, a pyrazolyl group, an imidazolyl group, a pyranyl group, a quinolyl group, a

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benzoxazolyl group, a benzothiazolyl group or a benzimidazolyl group (each of said phenyl, naphthyl, benzyl, pyridyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, pyranyl, quinolyl, benzoxazolyl, benzothiazolyl and benzimidazolyl groups may be substituted with at most 5 members selected from the group consisting of a hydroxyl group, a C₁-C₇ alkyl group, a C₁-C₇ alkoxy group and a halogen atom), a hydroxyl group or a halogen atom;

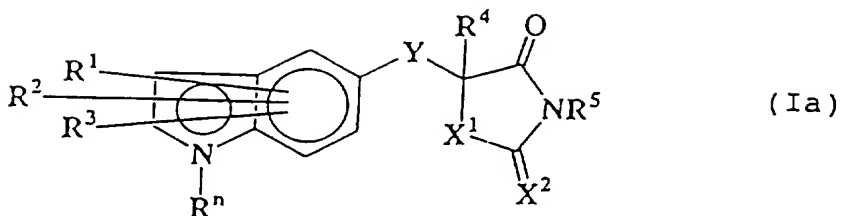
10 R⁴ is a hydrogen atom or a C₁-C₇ alkyl group, or forms a bond together with R⁷;

R⁵ is a hydrogen atom or a carboxymethyl group; and

Rⁿ is a substituent at the 1-position of an indole ring, and is a hydrogen atom, C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group, a C₁-C₄ alkoxymethyl group, an
15 aryloxymethyl group, a C₁-C₄ alkylaminomethyl group, a substituted acetamidemethyl group, a substituted thiomethyl group, a carboxyl group, a C₁-C₇ acyl group, an arylcarbonyl group, a C₁-C₄ alkoxycarbonyl group, an
20 aryloxy carbonyl group, a C₁-C₄ alkylaminocarbonyl group, an arylaminocarbonyl group, a C₁-C₇ alkoxy group, a C₁-C₇ alkoxyalkyloxy group, a trialkylsilyl group, a trialkylarylsilyl group, an alkylsulfonyl group or an arylsulfonyl group.

25 2. The indole type thiazolidine compound and its salt according to Claim 1, wherein the compound of the formula (I) is represented by the following formula (Ia):

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5
 wherein R^1 is a substituent at the 2-, 3-, 4-, 6- or 7-
 position of an indole ring and is a hydrogen atom, a C_1 -
 C_{10} alkyl group, a C_2 - C_{10} alkenyl group, a C_2 - C_{10} alkynyl
 group, a C_1 - C_{10} alkoxy group, a C_2 - C_{10} alkenyloxy group, a
 10 C_1 - C_{10} alkylthio group, a C_1 - C_{10} monoalkylamino group or a
 di- C_1 - C_{10} alkylamino group (each of said C_1 - C_{10} alkyl, C_2 -
 C_{10} alkenyl, C_2 - C_{10} alkynyl, C_1 - C_{10} alkoxy, C_2 - C_{10}
 alkenyloxy, C_1 - C_{10} alkylthio, C_1 - C_{10} monoalkylamino and
 di- C_1 - C_{10} alkylamino groups may be substituted with a
 15 hydroxyl group or a C_1 - C_7 alkyl group), or

- W_k - V_l -Z (among groups of Z as defined for the
 formula (I), said C_3 - C_{10} cycloalkyl group is cyclopropyl,
 cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl,
 cyclooctyl, cyclononyl, cyclodecyl, bicyclo[2.2.1]heptyl,
 20 bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, or adamantyl,
 said C_3 - C_7 cycloalkenyl group is cyclohexenyl,
 cyclopentadienyl, 2-bicyclo[2.2.1]heptenyl or 2,5-
 bicyclo[2.2.1]heptadienyl, said C_6 - C_{14} aromatic group is
 phenyl, naphthyl, indenyl, indanyl or fluorenyl, said C_1 -
 25 C_{12} heterocyclic aromatic group is furyl, thienyl,
 pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl,
 furazanyl, pyrazolyl, oxypyrazolyl, imidazolyl,

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oxoimidazolyl, triazolyl, triazolonyl, tetrazolyl, pyranyl, pyridyl, pyridonyl, pyridazinyl, pyridazinonyl, pyrimidinyl, pyrimidinonyl, pyrazinyl, triazinyl, tetrazinyl, indolyl, quinolyl, quinolonyl, benzofuranyl, benzothienyl, isoquinolyl, isoquinolonyl, benzoxazolyl, benzothiazolyl, benzopyrazolyl, benzimidazolyl, benzotriazolyl, benzopyranyl, indoliziny, purinyl, phthalazinyl, oxophthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzodioxolyl, benzodioxanyl, oxonaphthalenyl, dihydrobenzofuranyl, benzothiazinyl, pteridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[5,1-c][1,2,4]triazinyl, thiazolo[3,2-b]triazolyl, benzopyrano[2,3-b]pyridyl, 5H-benzopyrano[2,3-b]pyridonyl, xanthenyl, phenoxathiinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, or thianthrenyl, and said C₁-C₆ heterocycloaliphatic group is piperidyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, morpholinyl, or tetrahydrofuranyl, (each of said C₃-C₁₀ cycloalkyl, C₃-C₇ cycloalkenyl, C₆-C₁₄ aromatic, C₁-C₁₂ heterocyclic aromatic and C₁-C₆ heterocycloaliphatic groups may have at most 5 substituents selected from the group consisting of a hydrogen atom, a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group, a C₃-C₇ cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C₁-C₇ alkoxy group, a C₁-C₇ alkylthio group, a halogen atom, a

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trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C₁-C₃ alkoxy carbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C₁-C₇-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group, a C₁-C₃ alkoxy group, a C₁-C₃ alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group and a thiazolidindion-5-yl methyl group),

V is O, S, SO, SO₂ or NR⁸ (R⁸ is a hydrogen atom or a C₁-C₃ alkyl group),

W is a divalent C₁-C₆ saturated or C₂-C₆ unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C₁-C₇ alkyl groups, and

each of k and ℓ is 0 or 1),

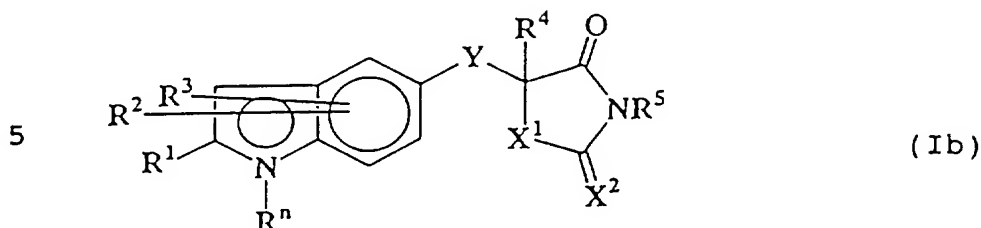
-V-W-Z (V, W and Z are as defined above), or

-W-V-W-Z (V, W and Z are as defined above, and two W's may be the same or different).

3. The indole type thiazolidine compound and its salt

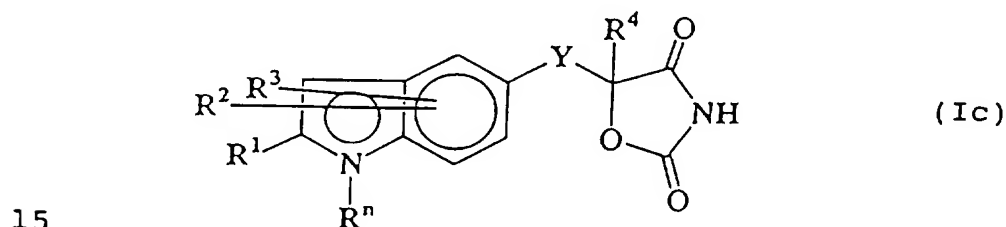
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according to Claim 2, wherein the compound of the formula (Ia) is represented by the formula (Ib):



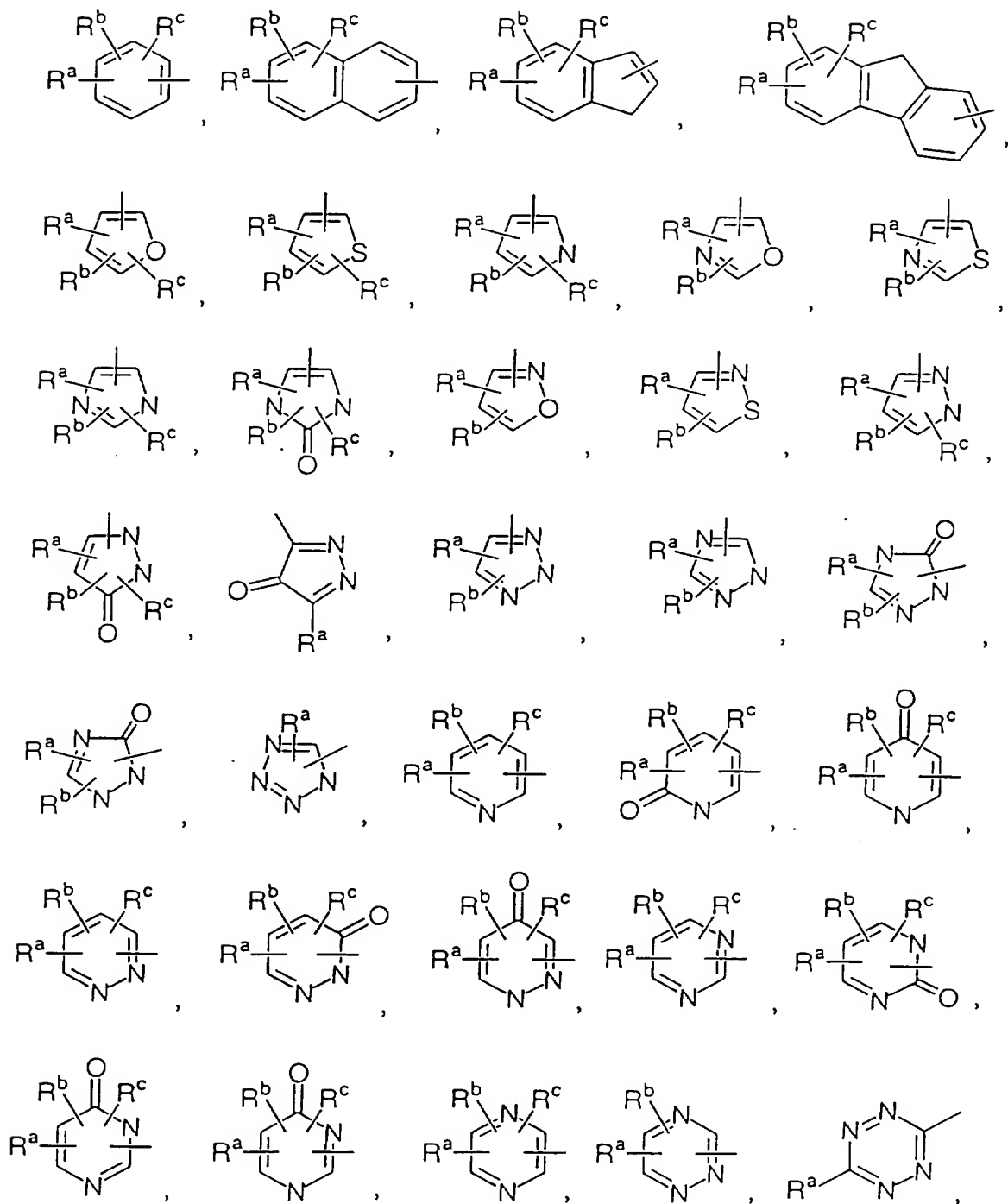
4. The indole type thiazolidine compound and its salt according to Claim 3, wherein the compound of the formula (Ib) is represented by the formula (Ic):

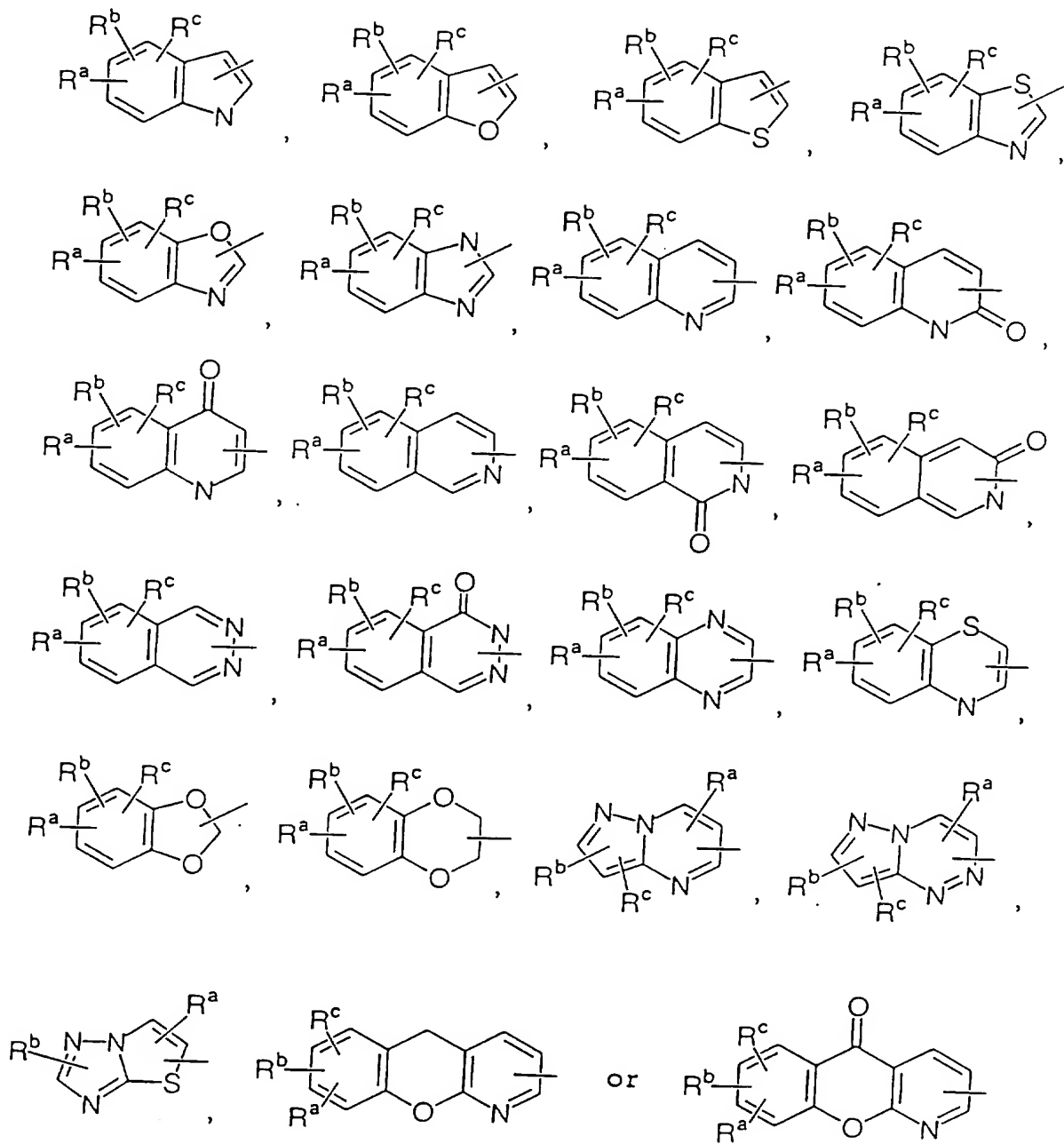
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wherein R^1 is a substituent at the 2-position of an indole ring, and is -W-Z, -V-Z, -W-V-Z, -V-W-Z or -W-V-W-Z (V is O, S, SO, SO₂ or NR⁸ (R⁸ is a hydrogen atom or a C₁-C₃ alkyl group), W is a divalent C₁-C₆ saturated or C₂-C₆ unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C₁-C₇ alkyl groups, when two W's are present, such W's may be the same or different, and Z is

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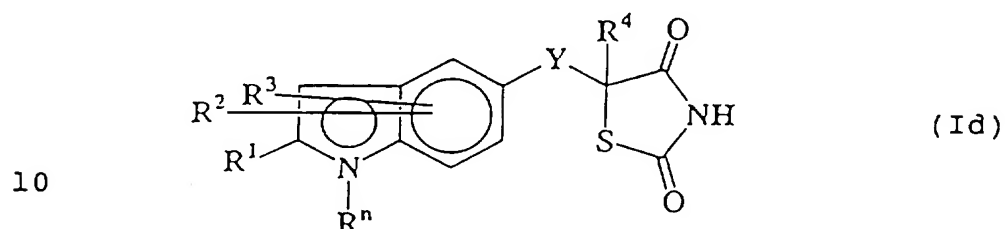
wherein each of R^a and R^b is independently a hydrogen atom, a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group, a C_3 - C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1 - C_7 alkoxy group, a C_1 - C_7 alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1 - C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri- C_1 - C_7 -alkylsilyloxy group, a phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group, a C_1 - C_3 alkoxy group, a C_1 - C_3 alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group or a hydroxymethyl group);

R^2 or R^3 is a hydrogen atom, a C_1 - C_4 alkyl group, a

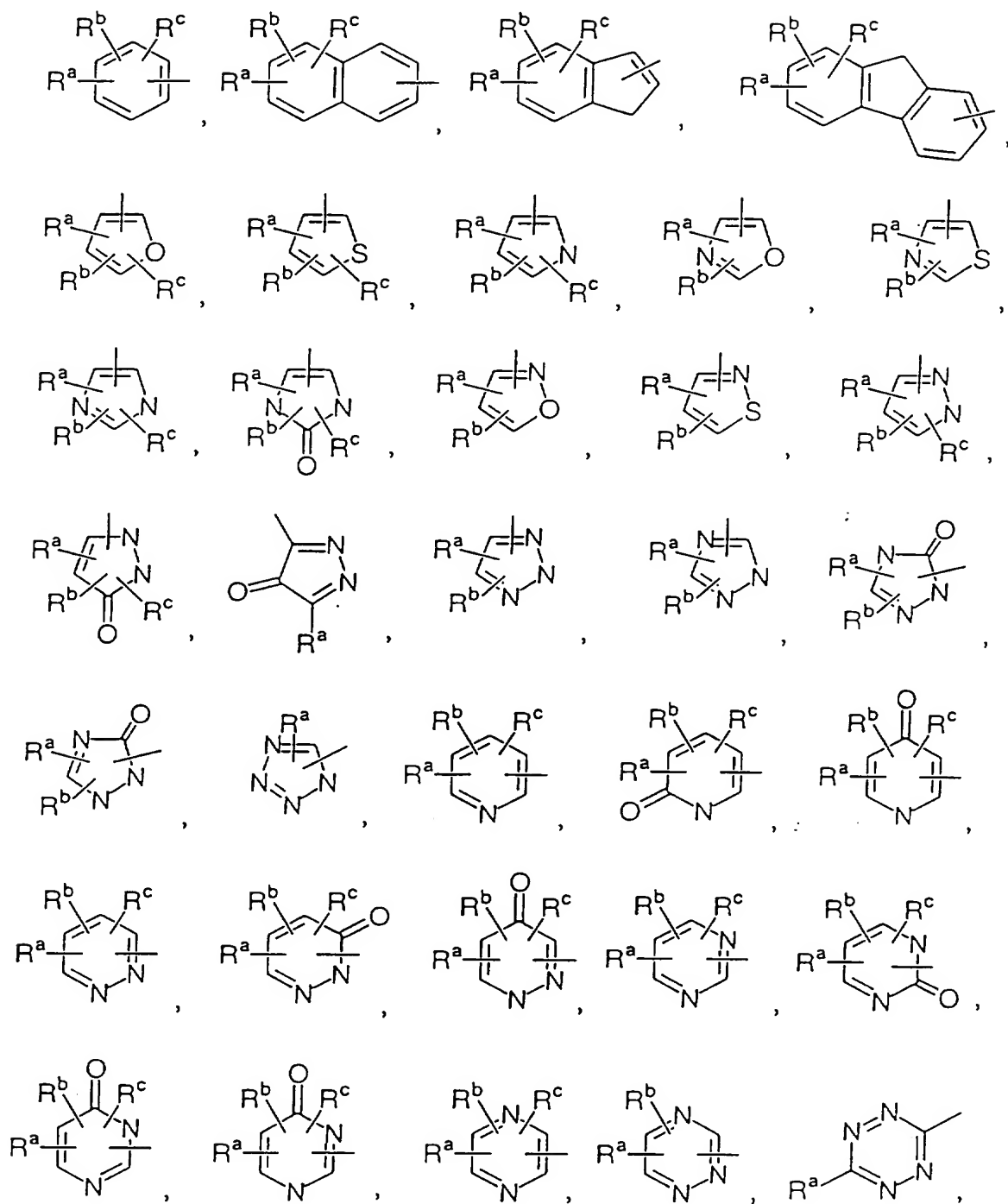
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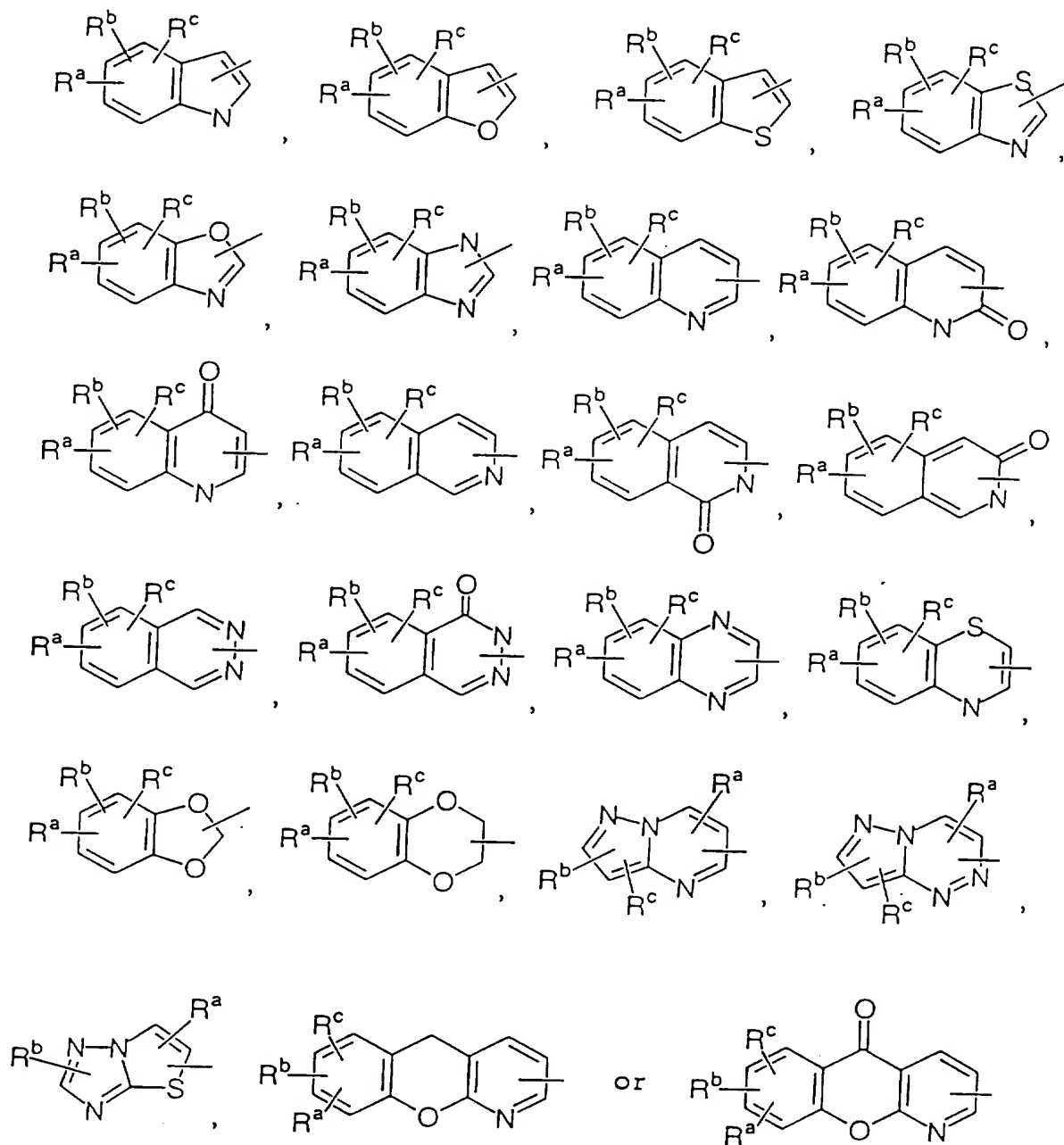
C₃-C₆ cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and R⁵ is a hydrogen atom.

5 The indole type thiazolidine compound and its salt according to Claim 3, wherein the compound of the formula (Ib) is represented by the formula (Id):



wherein R¹ is a substituent at the 2-position of an indole ring, and is -W-Z, -V-Z, -W-V-Z, -V-W-Z or -W-V-W-Z (V is O, S, SO, SO₂ or NR⁸ (R⁸ is a hydrogen atom or a C₁-C₃ alkyl group), W is a divalent C₁-C₆ saturated or C₂-C₆ unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C₁-C₇ alkyl groups, when two W's are present, such W's may be the same or different, and Z is





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wherein each of R^a and R^b is independently a hydrogen atom, a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group, a C_3 - C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1 - C_7 alkoxy group, a C_1 - C_7 alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1 - C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri- C_1 - C_7 -alkylsilyloxy group, a phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group, a C_1 - C_3 alkoxy group, a C_1 - C_3 alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group or a hydroxymethyl group);

R^2 or R^3 is a hydrogen atom, a C_1 - C_4 alkyl group, a

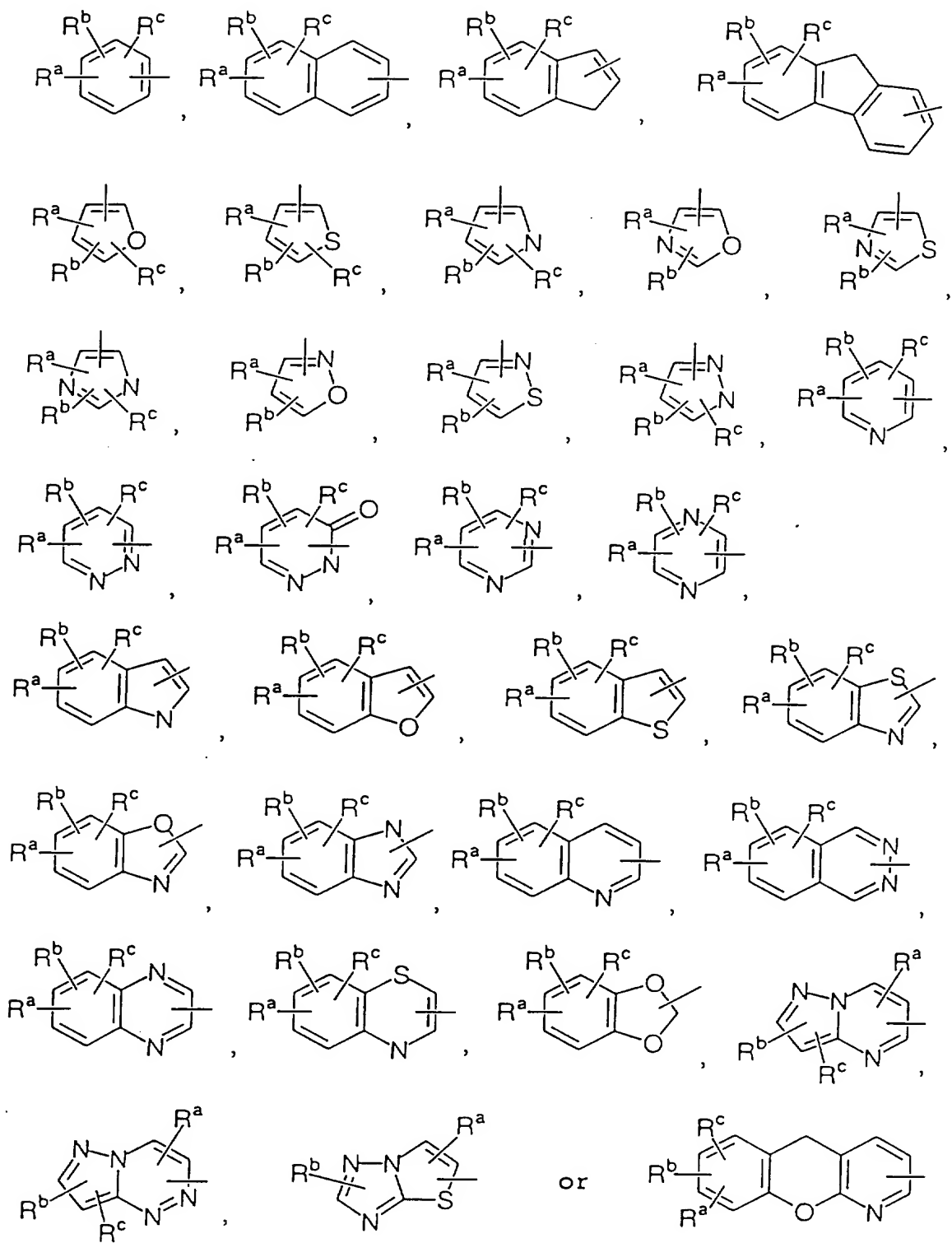
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C₃-C₆ cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and

R⁵ is a hydrogen atom.

6. The indole type thiazolidine compound and its salt
5 according to Claim 5, wherein Y is CR⁶R⁷ (R⁶ is a hydrogen atom or a methyl group, and R⁷ is a hydrogen atom, or forms a bond together with R⁴);

R¹ is a substituent at the 2-position of an indole ring, and is -W-Z, -V-Z, -W-V-Z, -V-W-Z or -W-V-W-Z (V is
10 O, S, SO, SO₂ or NR⁸ (R⁸ is a hydrogen atom or a C₁-C₃ alkyl group), W is a divalent C₁-C₆ saturated or C₂-C₆ unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C₁-C₇ alkyl groups (provided that the first carbon atom bonded to N is not
15 substituted with a hydroxyl group and the first carbon atom bonded to O is not substituted with a hydroxyl group or an oxo group), when two W's are present, such W's may be the same or different, and Z is



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wherein each R^a and R^b is independently a hydrogen atom, a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group, a C_3 - C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1 - C_7 alkoxy group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1 - C_3 alkoxy carbonyl group, a nitrile group, a carbamoyl group, a phenoxy group, a benzyloxy group, a tri- C_1 - C_7 -alkylsilyloxy group, a phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group, a C_1 - C_3 alkoxy group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group or a hydroxymethyl group);

R^4 is a hydrogen atom or a methyl group, or forms a bond together with R^7 ; and

R^n is a substituent at the 1-position of an indole

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ring, and is a hydrogen atom, a C₁-C₃ alkyl group, a cyclopropyl group, a C₁-C₂ alkoxymethyl group, a benzyloxymethyl group, a carboxyl group, a methoxycarbonyl group, a C₁-C₃ alkoxy group and a
 5 trialkylsilyl group.

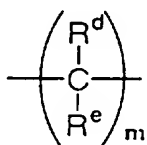
7. The indole type thiazolidine compound and its salt according to Claim 6, wherein:

R¹ is -W-Z, wherein W is a divalent C₁-C₆ saturated or C₂-C₆ unsaturated hydrocarbon group which may be
 10 substituted with at most 2 of hydroxyl, oxo and C₁-C₇ alkyl groups.

8. The indole type thiazolidine compound and its salt according to Claim 7, wherein:

R¹ is -W-Z, wherein W is

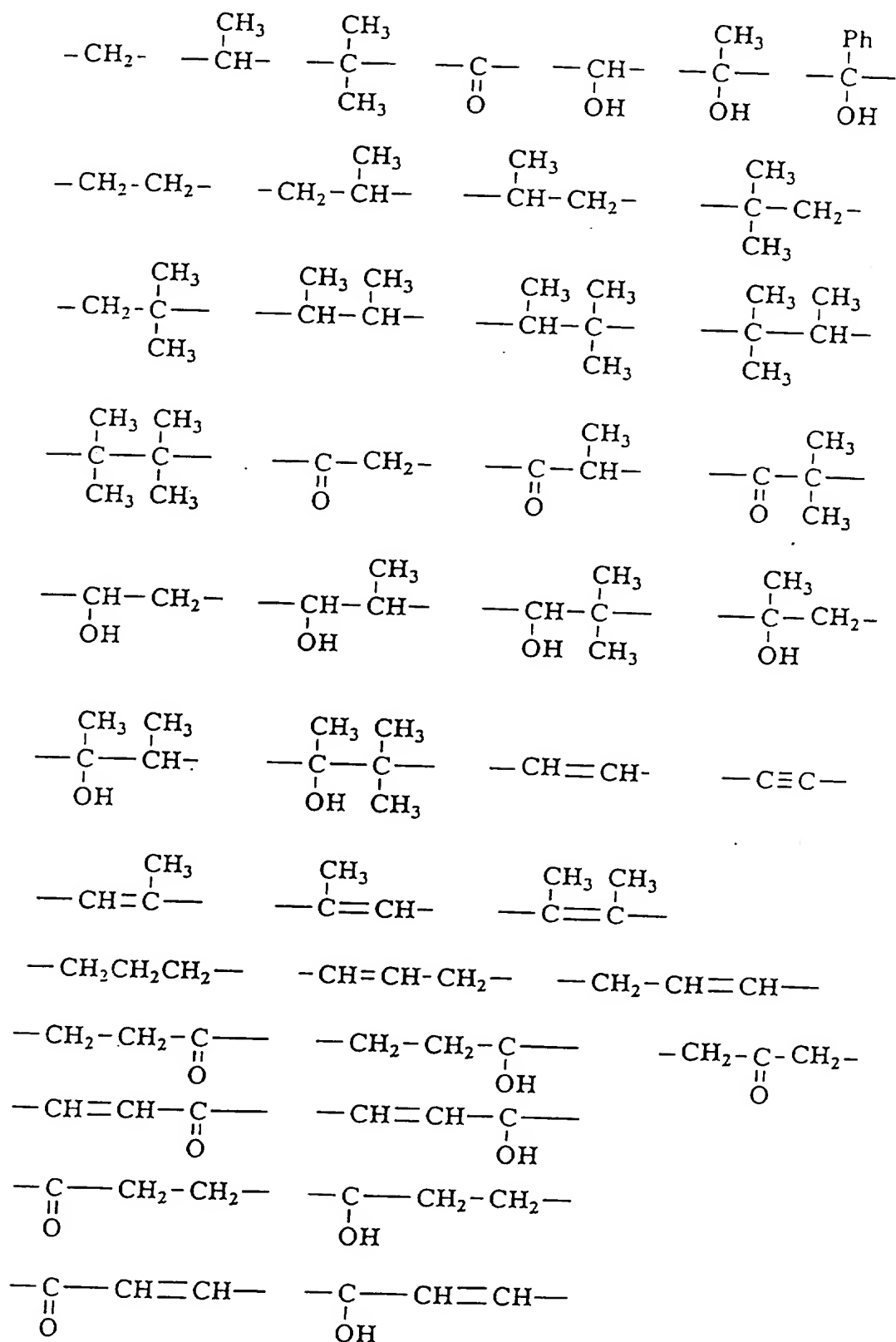
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wherein m is from 1 to 5, and each of R^d and R^e is independently a hydrogen atom, a methyl group or a
 20 hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d's together form a double bond, or adjacent R^d's and R^e's together form a triple bond.

9. The indole type thiazolidine compound and its salt according to Claim 8, wherein:

25 R¹ is -W-Z, wherein W is



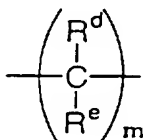
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10. The indole type thiazolidine compound and its salt according to Claim 6, wherein:

R^1 is $-V-Z$, wherein V is S, SO or SO_2 .

11. The indole type thiazolidine compound and its salt
5 according to Claim 6, wherein:

R^1 is $-W-V-Z$, wherein W is



10 wherein m is from 1 to 5, and each of R^d and R^e is independently a hydrogen atom, a methyl group or a hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d 's together form a double bond, or adjacent
15 R^d 's and R^e 's together form a triple bond (provided that R^d and R^e on the first carbon atom adjacent to N are not hydroxyl groups and also provided that R^d and R^e on the first carbon atom adjacent to O are not hydroxyl groups or do not together form an oxo group),

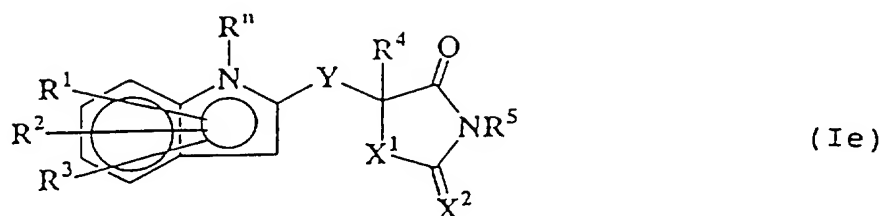
20 V is NR^8 (R^8 is a hydrogen atom or a C_1 - C_3 alkyl group).

12. The indole type thiazolidine compound and its salt according to Claim 11, wherein:

R^1 is $-W-V-Z$, wherein $-W-V-$ is $-CO-NR^8-$ (R^8 is a hydrogen atom or a C_1 - C_3 alkyl group).

25 13. The indole type thiazolidine compound and its salt according to Claim 1, wherein the compound of the formula (I) is represented by the following formula (Ie):

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- 5 wherein R^1 is a substituent at the 3-, 4-, 5-, 6- or 7-position of an indole ring, and is a C_1 - C_{10} alkyl group, a C_2 - C_{10} alkenyl group, a C_2 - C_{10} alkynyl group, a C_1 - C_{10} alkoxy group, a C_2 - C_{10} alkenyloxy group, a C_1 - C_{10} alkylthio group, a C_1 - C_{10} monoalkylamino group or a di-
- 10 C_1 - C_{10} alkylamino group (each of said C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, C_1 - C_{10} alkoxy, C_2 - C_{10} alkenyloxy, C_1 - C_{10} alkylthio, C_1 - C_{10} monoalkylamino and di- C_1 - C_{10} alkylamino groups may be substituted with a hydroxyl group or a C_1 - C_7 alkyl group), or
- 15 $-W_k-V_\ell-Z$ (among groups of Z as defined for the formula (I), said C_3 - C_{10} cycloalkyl group is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, or adamantyl,
- 20 said C_3 - C_7 cycloalkenyl group is cyclohexenyl, cyclopentadienyl, 2-bicyclo[2.2.1]heptenyl or 2,5-bicyclo[2.2.1]heptadienyl, said C_6 - C_{14} aromatic group is phenyl, naphthyl, indenyl, indanyl or fluorenyl, said C_1 - C_{12} heterocyclic aromatic group is furyl, thienyl,
- 25 pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, furazanyl, pyrazolyl, oxypyrazolyl, imidazolyl, oxoimidazolyl, triazolyl, triazolonyl, tetrazolyl,

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pyranyl, pyridyl, pyridonyl, pyridazinyl, pyridazinonyl, pyrimidinyl, pyrimidinonyl, pyrazinyl, triazinyl, tetrazinyl, indolyl, quinolyl, quinolonyl, benzofuranyl, benzothienyl, isoquinolyl, isoquinolonyl, benzoxazolyl, benzothiazolyl, benzopyrazolyl, benzimidazolyl, benzotriazolyl, benzopyranyl, indoliziny, purinyl, phthalazinyl, oxophthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzodioxolyl, benzodioxanyl, oxonaphthalenyl, dihydrobenzofuranyl, benzothiazinyl, pteridinyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[5,1-c][1,2,4]triazinyl, thiazolo[3,2-b]triazolyl, benzopyrano[2,3-b]pyridyl, 5H-benzopyrano[2,3-b]pyridonyl, xanthenyl, phenoxathiinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, or thianthrenyl, and said C₁-C₆ heterocycloaliphatic group is piperidyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, morpholinyl, or tetrahydrofuranyl, (each of said C₃-C₁₀ cycloalkyl, C₃-C₇ cycloalkenyl, C₆-C₁₄ aromatic, C₁-C₁₂ heterocyclic aromatic and C₁-C₆ heterocycloaliphatic groups may have at most 5 substituents selected from the group consisting of a hydrogen atom, a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group, a C₃-C₇ cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C₁-C₇ alkoxy group, a C₁-C₇ alkylthio group, a halogen atom, a trifluoromethyl group, a nitro group, an amino group, a

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methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C₁-C₃ alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri-C₁-C₇-alkylsilyloxy group, a phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group, a C₁-C₃ alkoxy group, a C₁-C₃ alkylthio group, a hydroxyl group, a halogen atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group and a thiazolidindion-5-yl methyl group),

V is O, S, SO, SO₂ or NR⁸ (R⁸ is a hydrogen atom or a C₁-C₃ alkyl group),

W is a divalent C₁-C₆ saturated or C₂-C₆ unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C₁-C₇ alkyl groups, and each of k and ℓ is 0 or 1),

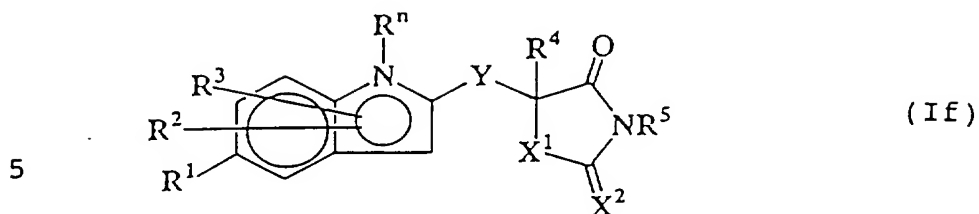
-V-W-Z (V, W and Z are as defined above), or

-W-V-W-Z (V, W and Z are as defined above, and two W's may be the same or different).

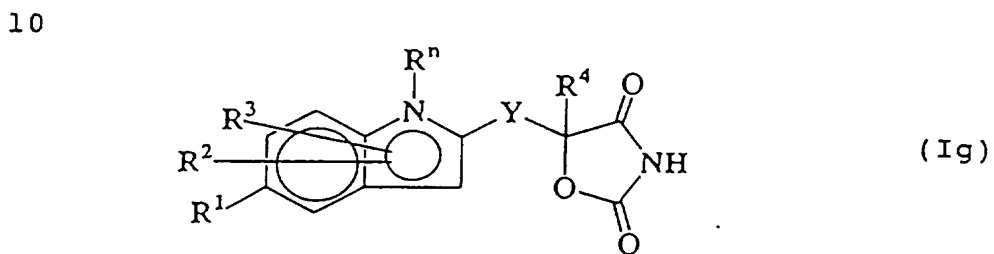
14. The indole type thiazolidine compound and its salt according to Claim 13, wherein the compound of the

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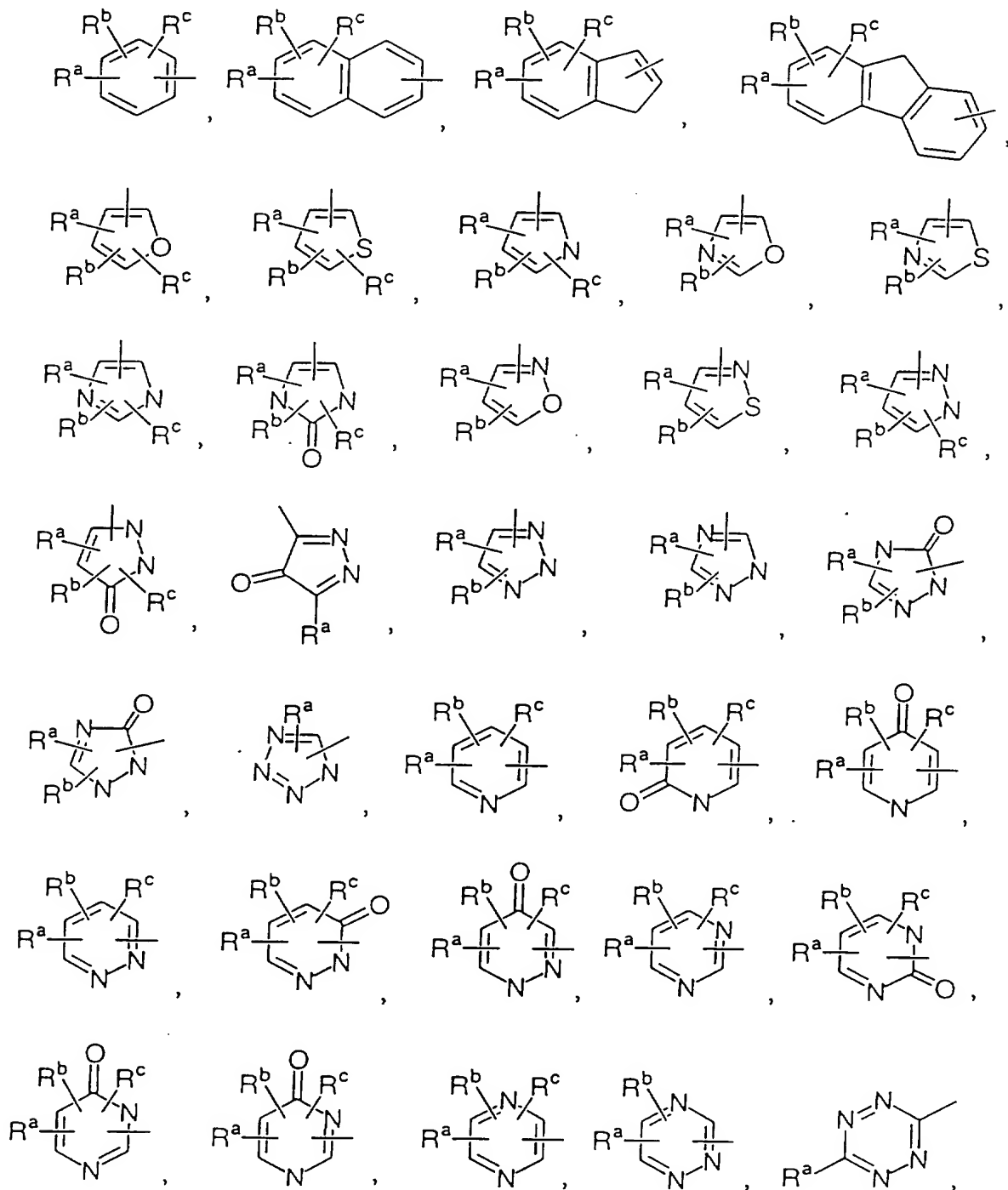
formula (Ie) is represented by the formula (If):

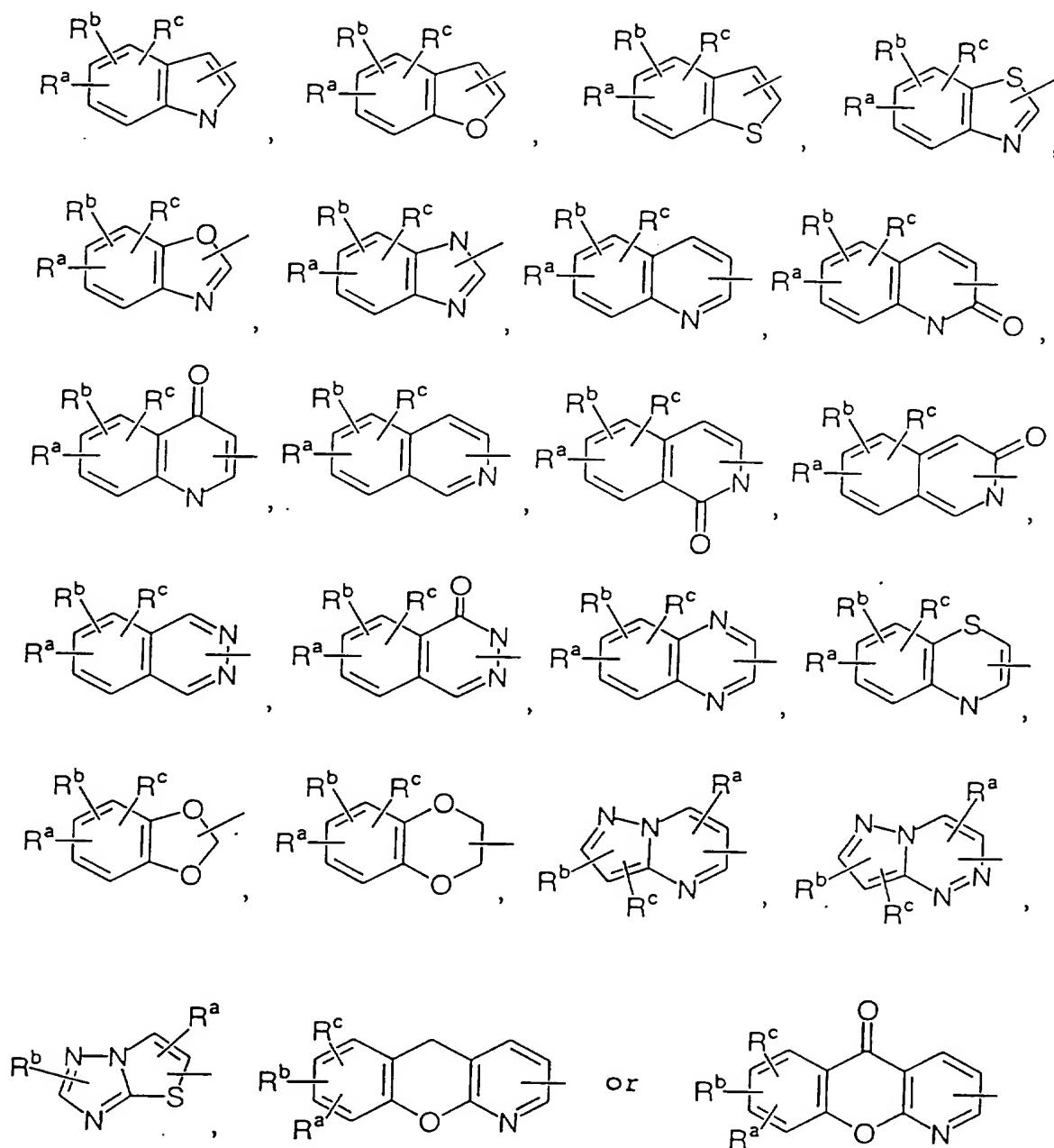


15. The indole type thiazolidine compound and its salt according to Claim 14, wherein the compound of the formula (If) is represented by the formula (Ig):



15 wherein R^1 is a substituent at the 5-position of an indole ring, and is $-W-Z$, $-V-Z$, $-W-V-Z$, $-V-W-Z$ or $-W-V-W-Z$ (V is O , S , SO , SO_2 or NR^8 (R^8 is a hydrogen atom or a C_1 - C_3 alkyl group), W is a divalent C_1 - C_6 saturated or C_2 - C_6 unsaturated hydrocarbon group which
20 may be substituted with at most 3 of hydroxyl, oxo and C_1 - C_7 alkyl groups, when two W 's are present, such W 's may be the same or different, and Z is





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wherein each of R^a and R^b is independently a hydrogen atom, a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group, a C_3 - C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1 - C_7 alkoxy group, a C_1 - C_7 alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1 - C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri- C_1 - C_7 -alkylsilyloxy group, a phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group, a C_1 - C_3 alkoxy group, a C_1 - C_3 alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group or a hydroxymethyl group);

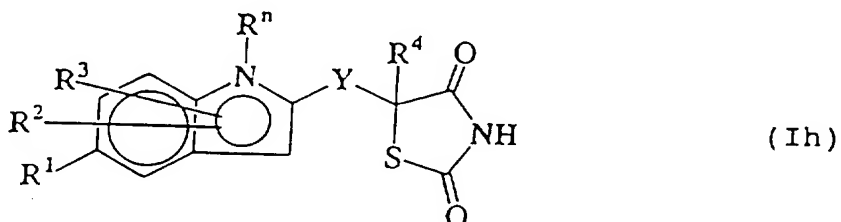
R^2 or R^3 is a hydrogen atom, a C_1 - C_4 alkyl group, a

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C₃-C₆ cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and

R⁵ is a hydrogen atom.

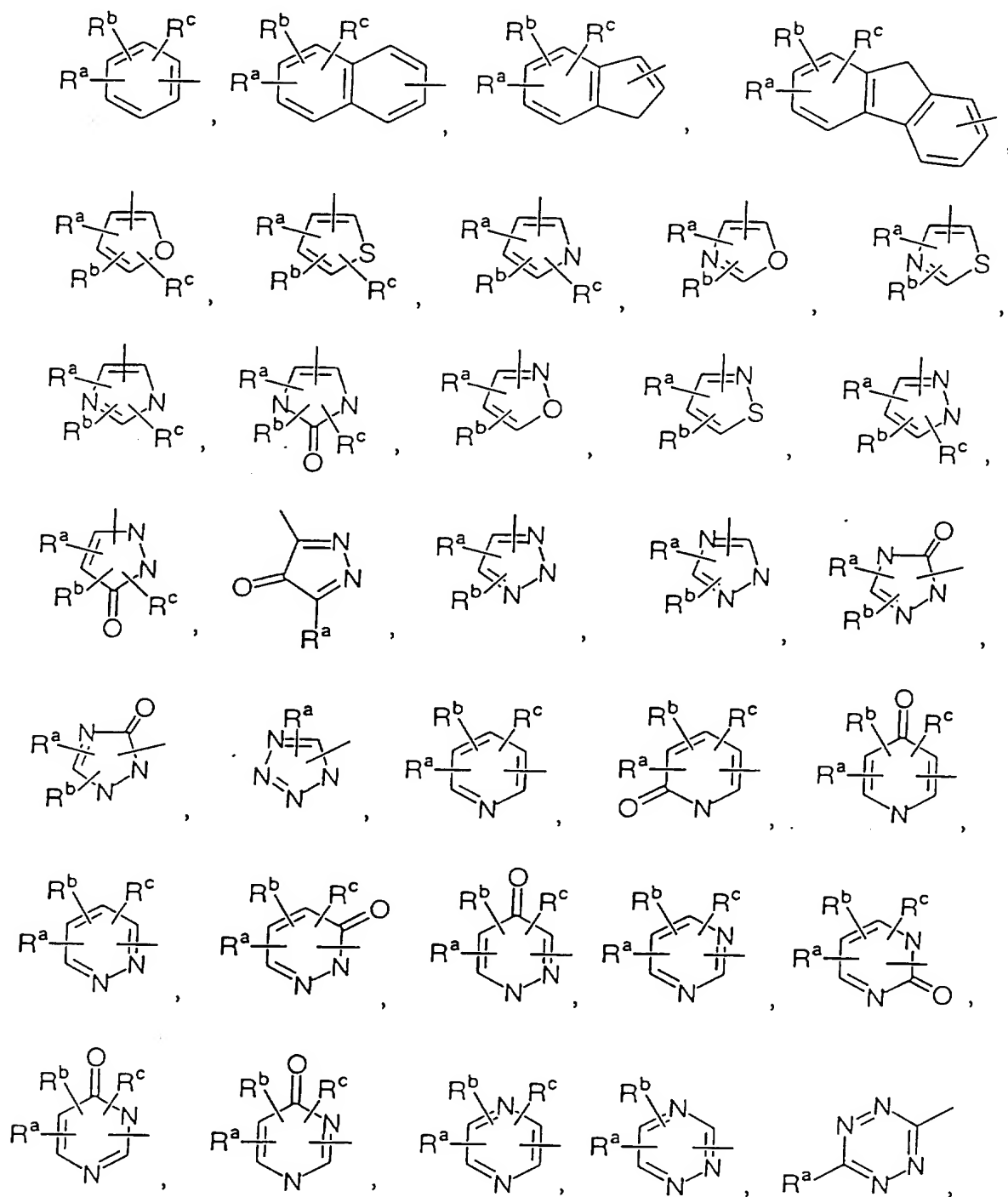
16. The indole type thiazolidine compound and its salt according to Claim 14, wherein the compound of the formula (If) is represented by the formula (Ih):

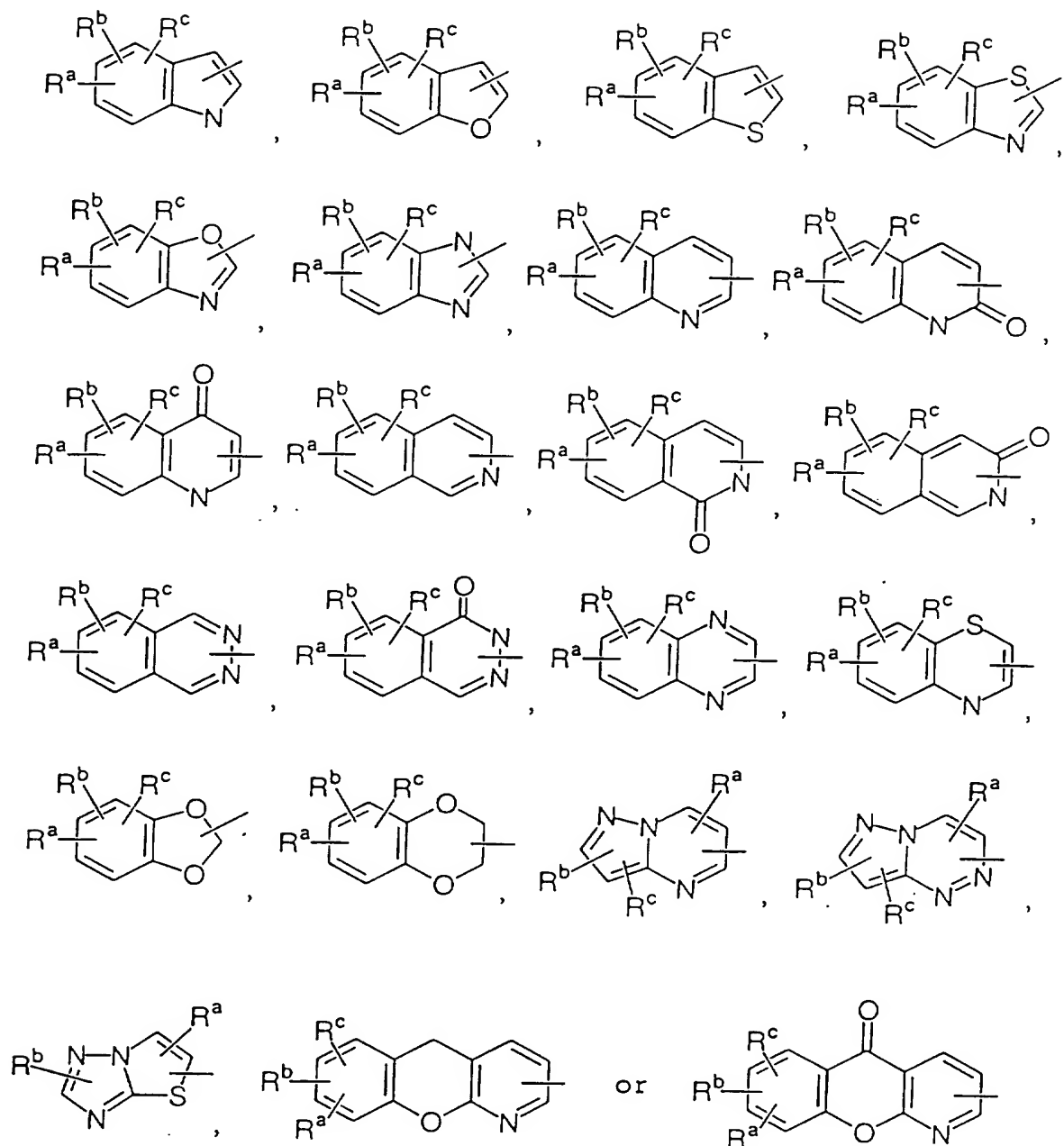


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wherein R¹ is a substituent at the 5-position of an indole ring, and is -W-Z, -V-Z, -W-V-Z, -V-W-Z or -W-V-W-Z (V is O, S, SO, SO₂ or NR⁸ (R⁸ is a hydrogen atom or a C₁-C₃ alkyl group), W is a divalent C₁-C₆ saturated or C₂-C₆ unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C₁-C₇ alkyl groups, when two W's are present, such W's may be the same or different, and Z is

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wherein each of R^a and R^b is independently a hydrogen atom, a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group, a C_3 - C_7 cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C_1 - C_7 alkoxy group, a C_1 - C_7 alkylthio group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C_1 - C_3 alkoxycarbonyl group, a nitrile group, a carbamoyl group, a sulfamoyl group, a phenoxy group, a benzyloxy group, a tri- C_1 - C_7 -alkylsilyloxy group, a phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group, a C_1 - C_3 alkoxy group, a C_1 - C_3 alkylthio group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 1-tetrazolyl group, a 3-tetrazolyl group, a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C_1 - C_7 alkyl group, a C_3 - C_7 cycloalkyl group or a hydroxymethyl group);

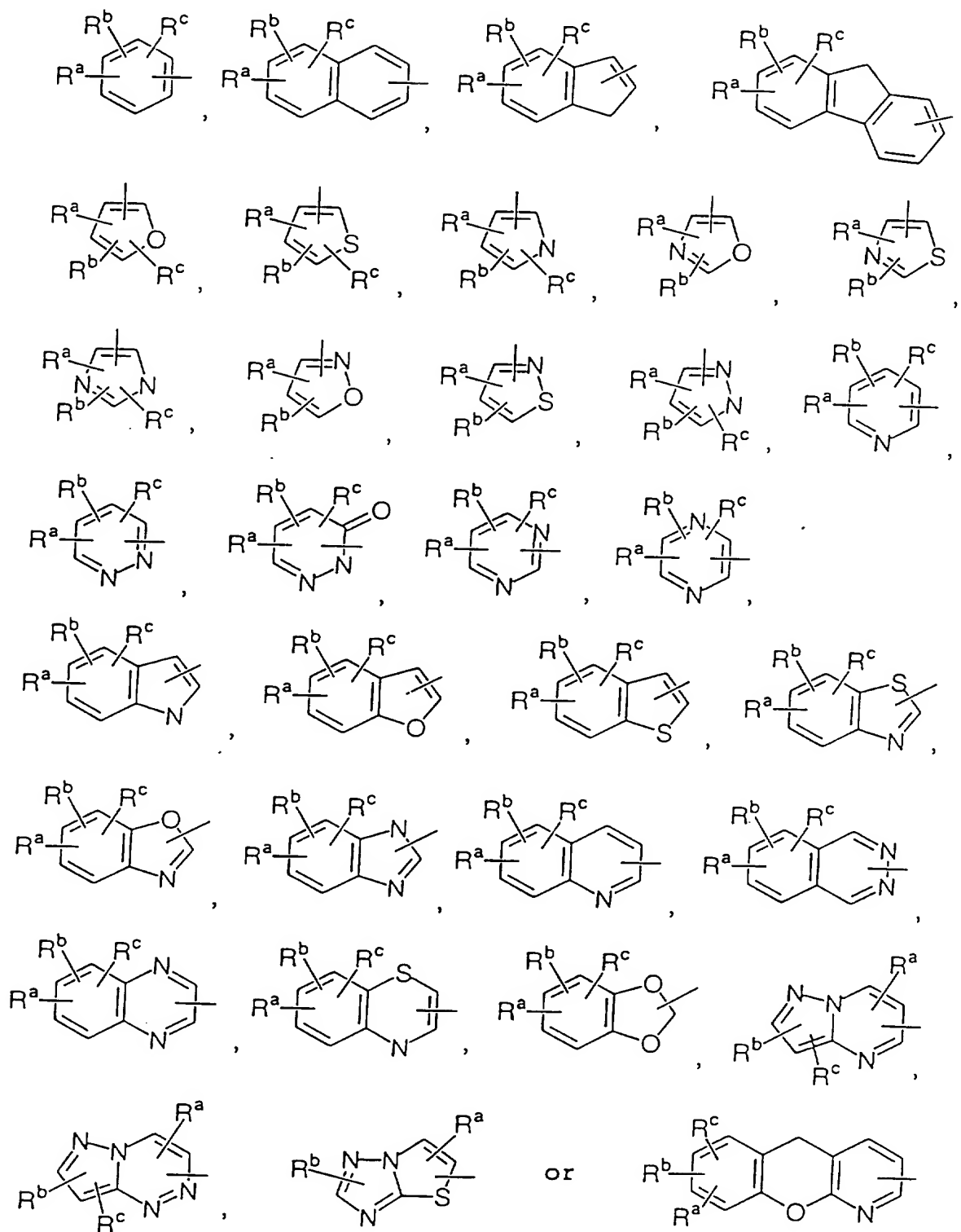
R^2 or R^3 is a hydrogen atom, a C_1 - C_4 alkyl group, a

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C₃-C₆ cycloalkyl group, a phenyl group, a naphthyl group, a benzyl group, a pyridyl group or a halogen atom; and R⁵ is a hydrogen atom.

17. The indole type thiazolidine compound and its salt according to Claim 16, wherein Y is CR⁶R⁷ (R⁶ is a hydrogen atom or a methyl group, and R⁷ is a hydrogen atom, or forms a bond together with R⁴);

R¹ is a substituent at the 5-position of an indole ring, and is -W-Z, -V-Z, -W-V-Z, -V-W-Z or -W-V-W-Z (V is O, S, SO, SO₂ or NR⁸ (R⁸ is a hydrogen atom or a C₁-C₃ alkyl group), W is a divalent C₁-C₆ saturated or C₂-C₆ unsaturated hydrocarbon group which may be substituted with at most 3 of hydroxyl, oxo and C₁-C₇ alkyl groups (provided that the first carbon atom bonded to N is not substituted with a hydroxyl group and the first carbon atom bonded to O is not substituted with a hydroxyl group or an oxo group), when two W's are present, such W's may be the same or different, and Z is



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wherein each R^a and R^b is independently a hydrogen atom, a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group, a C₃-C₇ cycloalkenyl group (said alkyl, cycloalkyl and cycloalkenyl groups may be substituted with a hydroxyl group), a hydroxyl group, a C₁-C₇ alkoxy group, a fluorine atom, a chlorine atom, a bromine atom, a trifluoromethyl group, a nitro group, an amino group, a methylamino group, a dimethylamino group, an acetamide group, a methanesulfonylamide group, a carboxyl group, a C₁-C₃ alkoxycarbonyl group, a nitrile group, a carbamoyl group, a phenoxy group, a benzyloxy group, a tri-C₁-C₇-alkylsilyl group, a phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl or benzyl group (each of said phenyl, α -naphthyl, β -naphthyl, furanyl, thienyl, imidazolyl, pyridyl and benzyl groups may be substituted with at most 5 substituents selected from the group consisting of a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group, a C₁-C₃ alkoxy group, a hydroxyl group, a fluorine atom, a chlorine atom, a bromine atom, a nitro group and a dimethylamino group), a 5-tetrazolyl group, a thiazolidindion-5-yl group or a thiazolidindion-5-yl methyl group, and R^c is a hydrogen atom, a C₁-C₇ alkyl group, a C₃-C₇ cycloalkyl group or a hydroxymethyl group);

R⁴ is a hydrogen atom or a methyl group, or forms a bond together with R⁷; and

Rⁿ is a substituent at the 1-position of an indole

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ring, and is a hydrogen atom, a C₁-C₃ alkyl group, a cyclopropyl group, a C₁-C₂ alkoxymethyl group, a benzyloxymethyl group, a carboxyl group, a methoxycarbonyl group, a C₁-C₃ alkoxy group and a
 5 trialkylsilyl group.

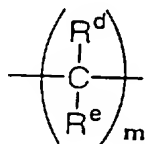
18. The indole type thiazolidine compound and its salt according to Claim 17, wherein:

R¹ is -W-Z, wherein W is a divalent C₁-C₆ saturated or C₂-C₆ unsaturated hydrocarbon group which may be
 10 substituted with at most 2 of hydroxyl, oxo and C₁-C₇ alkyl groups.

19. The indole type thiazolidine compound and its salt according to Claim 18, wherein:

R¹ is -W-Z, wherein W is

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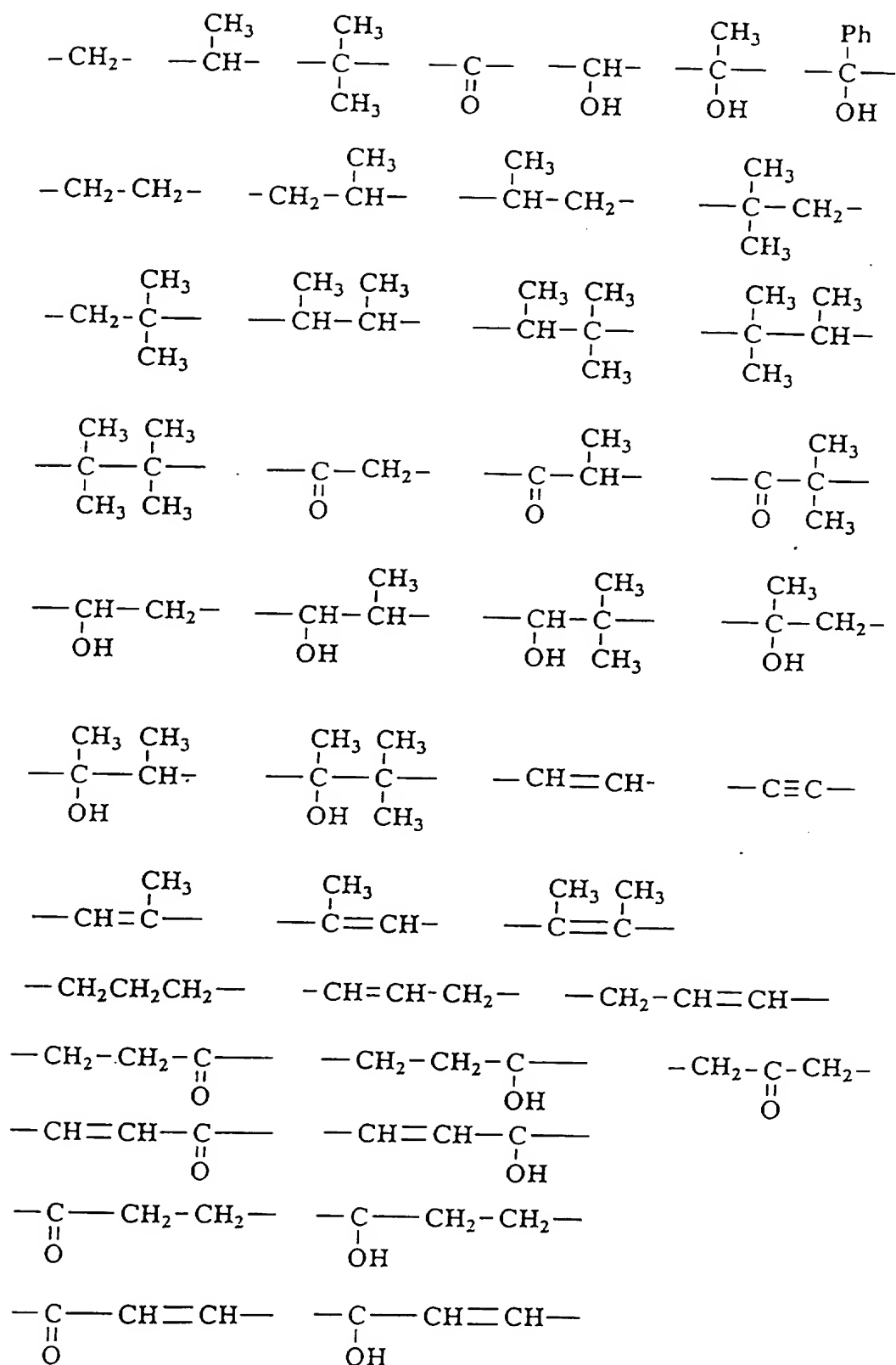


wherein m is from 1 to 5, and each of R^d and R^e is independently a hydrogen atom, a methyl group or a
 20 hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d's together form a double bond, or adjacent R^d's and R^e's together form a triple bond.

20. The indole type thiazolidine compound and its salt according to Claim 19, wherein:

25 R¹ is -W-Z, wherein W is

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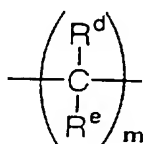
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21. The indole type thiazolidine compound and its salt according to Claim 17, wherein:

R^1 is -V-Z, wherein V is S, SO or SO_2 .

22. The indole type thiazolidine compound and its salt
5 according to Claim 17, wherein:

R^1 is -W-V-Z, wherein W is



10 wherein m is from 1 to 5, and each of R^d and R^e is independently a hydrogen atom, a methyl group or a hydroxyl group, or R^d and R^e together form an oxo group, or adjacent R^d 's together form a double bond, or adjacent R^d 's and R^e 's together form a triple bond (provided that
15 R^d and R^e on the first carbon atom adjacent to N are not hydroxyl groups and also provided that R^d and R^e on the first carbon atom adjacent to O are not hydroxyl groups or do not together form an oxo group), and

20 V is NR^8 (R^8 is a hydrogen atom or a C_1 - C_3 alkyl group).

23. The indole type thiazolidine compound and its salt according to Claim 22, wherein:

R^1 is -W-V-Z, wherein -W-V- is $-CO-NR^8-$ (R^8 is a hydrogen atom or a C_1 - C_3 alkyl group).

25 24. The indole type thiazolidine compound and its salt according to Claim 9, 10, 12, 20, 21 or 22, wherein:

Y is $-CH_2-$; and

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R^4 is a hydrogen atom.

25. The indole type thiazolidine compound and its salt according to Claim 9, 10, 12, 20, 21 or 22, wherein:

Y is CHR^7 (R^7 forms a bond together with R^4); and

5 R^4 forms a bond together with R^7 .

26. A hypoglycemic agent containing the indole type thiazolidine compound or its salt according to Claim 1 as an active agent.

27. An aldose reductase inhibitor containing the indole
10 type thiazolidine compound or its salt according to Claim 1 as an active agent.

28. A pharmaceutical agent for preventing and treating diabetes mellitus and diabetic complications, which contains the indole type thiazolidine compound or its salt according to Claim 1 as an active agent.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 96/00403

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D417/06 C07D413/06 C07D417/14 A61K31/425 A61K31/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

13 May 1996

Date of mailing of the international search report

23.05.1996

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Fax (+ 31-70) 340-3016

Authorized officer

Henry, J

INTERNATIONAL SEARCH REPORT

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